

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**AFFIDAVIT OF STANLEY BUKOFZER, M.B., B.Ch., M. Med. (Int. Med.)**

I, Stanley Bukofzer, hereby declare and say:

1. My name is Stanley Bukofzer. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

**Education and Professional Background**

2. I am currently employed by Astellas Pharma U.S., Inc. as Vice President of Medical Affairs. From 1996 until June 2007, I was employed by Abbott Laboratories ("Abbott").
3. I was born in South Africa. I received my undergraduate degree as Bachelor of Medicine and Bachelor of Surgery from the University of Witwatersrand in

Johannesburg, South Africa in 1979. I subsequently specialized in internal medicine and received my postgraduate medical degree as Master of Medicine from the University of Witwatersrand in 1986. I was in academics and private practice until joining Abbott in mid-1996 as Medical Director for Abbott's South African affiliate, part of Abbott's International Division.

4. At the end of 1998, I was transferred to the Abbott International Division in Abbott Park, Illinois, as Associate Medical Director for Urological Products and later promoted to Medical Director. I remained in that position until approximately late March or early April 2001, when I was appointed Head of Abbott's Anti-Infective Venture. In August or September 2003, as a result of a change in company structure, I was named Global Project Head for Anti-Infectives. My role remained substantially the same as they had been in my previous position. In August or September 2004, I was promoted to Divisional Vice President of Global Medical Affairs, the position in which I remained until I left Abbott in 2006 to take up my present position.

#### Responsibilities as Head of Abbott's Anti-Infective Venture

5. When I became Head of the Anti-Infective Venture in March or April 2001, the venture had two compounds under development: (1) ABT-773, a ketolide antibiotic; and (2) ABT-492, a quinolone antibiotic. It was my responsibility as venture head to supervise and lead the team of professionals responsible for the development of these compounds. Among other things, my responsibility involved supervising Abbott's ABT-773 clinical study program and Abbott's efforts to receive approval of ABT-773 from the FDA and other regulatory agencies by ensuring that the benefit-to-risk ratio of the compound met the requirements of these agencies. It was also my responsibility to make



presentations regarding the status and development of ABT-773 to Abbott's senior management, including at meetings of the Pharmaceutical Executive Committee ("PEC") and at portfolio reviews.

6. I was informed that I would become Head of the Anti-Infective Venture several weeks before taking over that position. From the time in February 2001 when I was told that I was going to be appointed Head of the Anti-Infective Venture through at least mid-2002, I spent an average of more than 50% of my time on ABT-773-related work.

7. In order to be able to fulfill my duties and responsibilities in supervising the development of ABT-773, during the transitional period of the last week of February and March 2001, prior to becoming venture head I worked to familiarize myself with the status of the compound. In order to do so, I read documents regarding the history, status and development of ABT-773 provided to me.

8. During this transitional period, I reviewed materials provided to me by my future boss, Dr. Eugene Sun, Abbott's Divisional Vice President for Anti-Viral and Anti-Infective Development, and by a few members of the existing ABT-773 team in order to allow me to become familiar with the program for which I would soon be responsible. For example, by email dated February 22, 2001, Dr. Sun sent me several key documents prepared by Abbott's ABT-773 team, including (1) Abbott's ABT-773 Development Plan; (2) an ABT-773 "Update" memorandum; (3) an ABT-773 Update presentation by the ABT-773 program to Abbott's senior management dated February 12, 2001; (4) an ABT-773 Portfolio Review presentation dated December 5, 2000; (5) a Contact Report regarding the ABT-773 End of Phase 2 Meeting with the FDA, held on November 27, 2000; and (6) Abbott's November 27, 2000 ABT-773 End of Phase 2 presentation to the

FDA. I read each of these documents after I received them. Attached hereto as D's Exhibit 608 is a true and correct copy of Dr. Sun's email to me of February 22, 2001, together with the documents that were attached to the email. I reviewed each of the documents regarding ABT-773 I received during this transitional period from Dr. Sun and other Abbott employees in detail.

9. During the week before I assumed leadership of the Anti-Infective Venture, I also met extensively with experienced members of the existing ABT-773 team to learn as much as I could about the status and development of the compound. For example, I met with Dr. Carl Craft, my predecessor as Head of the Anti-Infective Venture, for approximately three hours per day over a period of about a week, to obtain as much information from him as I could regarding the ABT-773 development program and the functioning of the venture. I also met with Dr. Craft's direct reports who were to become my direct reports, including Dr. Linda Swanson, at that time the director of the ABT-773 clinical research team to whom the project managers reported; Carol Meyer, the director of operations for ABT-773, who also additionally later assumed Dr. Swanson's responsibilities; and all of the medical directors for the ABT-773 program. Soon after becoming venture head, I also met with Jeanne Fox and Greg Bosco of Abbott's regulatory affairs group to discuss the status of ABT-773, Abbott's contacts with the FDA regarding ABT-773, and the regulatory environment in which ABT-773 was being developed. I also met with Rod Mittag of Abbott's commercial group with regard to ABT-773. I relied upon the information I received from these discussions with members of the ABT-773 team in fulfilling my responsibilities in the ordinary course of business as Head of the Anti-Infective Venture and in supervising the development of ABT-773.

10. In order to fulfill my duties and responsibilities as Head of the Anti-Infective Venture to supervise the development of ABT-773, I needed to become and stay fully informed of the status and of all significant developments with regard to the ABT-773 program. As a result of my extensive discussions and meetings with Abbott employees regarding ABT-773 and my review of key ABT-773 documents during February, March and April 2001, at the time I became Head of the Anti-Infective Venture in April I was and considered myself generally well informed with regard to the status and development of ABT-773 at that time and with the major issues that needed to be addressed as part of the ABT-773 development program, including clinical and regulatory questions, among others. During my tenure as venture head, I continued to meet on a daily basis with members of the ABT-773 team and to review documents and data regarding all aspects of the program. I relied upon the information I received in the ordinary course of business from the ABT-773 team and from ABT-773 documents both before and after I became venture head in my work and decision-making regarding the ABT-773 program and in meetings with and to make presentations to Abbott's senior management with respect to the status of and developments on the program.

11. As Head of the Anti-Infective Venture in 2001 and 2002, I reported directly to Dr. Sun, who in turn reported to Dr. John Leonard.

12. The Anti-Infective Venture employees reporting directly to me as the supervisor of the ABT-773 program included the head of the ABT-773 clinical team (Dr. Swanson), the head of the ABT-773 operations team (Ms. Meyer), and the medical directors. Other Abbott employees who worked on the ABT-773 team and reported to me indirectly or on a "dotted-line" as part of the matrixed team included chemists who worked to develop the

drug substance and the formulation of the compound, microbiologists and regulatory experts, including Jeanne Fox, the head of Abbott's Anti-Infective Regulatory Affairs group, as well as representatives of other functions.

13. Prior to and during most of the time I was responsible for supervising the development of ABT-773 during 2001 and 2002, the venture regularly generated in the ordinary course of business monthly reports that updated the status of the development of ABT-773. The monthly report for ABT-773 was prepared and circulated at the end of each month. Thus, for example, the March 2001 monthly report would have been prepared and circulated at the end of March 2001. The monthly status reports were usually prepared by Carol Meyer in her capacity as head of ABT-773 operations, with input from other members of the ABT-773 team. I did not prepare the monthly status reports myself, but it was my practice as venture head to review in the ordinary course of business each of the monthly status reports before they were finalized and to ensure that they were accurate and complete to the best of my knowledge. Attached hereto as D's Exhibits 613, 638 and 654 are what I believe to be true and correct copies of examples of the ABT-773 monthly status reports that I reviewed in performing my duties as venture head, from April 2001. These examples are for March 2001 (D's Exhibit 613), May 2001 (D's Exhibit 638), and July 2001 (D's Exhibit 654), respectively. Reports in the same or similar format were generated by the ABT-773 program in the ordinary course of business before I became venture head, and I reviewed and relied upon some of these earlier monthly status reports as part of the process in February and March 2001 of becoming informed about the status and development of ABT-773, as described above.

ABT-773: Status and Development As of April 2001

14. ABT-773 is a member of the new ketolide class of antibiotics, which is in turn related to the macrolide family of antibiotics. As Head of the Anti-Infective Venture, I learned that antibiotics is a competitive field, in which macrolides and quinolones compete against older forms of antibiotics, such as cephalosporins, erythromycin and penicillin, for the treatment of community acquired microbial infections.

15. I understand that ABT-773 was approved by Abbott's senior management in March 1997 as a candidate for development by Abbott's Anti-Infective Venture. When I became Head of the Anti-Infective Venture, the ABT-773 adult oral formulation program had entered into Phase III of the compound's development, though certain Phase I and Phase II trials regarding aspects of the program were still in progress or were being planned.

16. At the time that I became Head of the Anti-Infective Venture, the ABT-773 adult oral formulation was being developed for four indications: (1) Acute Bacterial Exacerbation of Chronic Bronchitis ("ABECB"); (2) Acute Bacterial Sinusitis ("ABS"); (3) Acute Streptococcal Pharyngitis/Tonsillitis ("Pharyngitis"); and (4) Community Acquired Pneumonia ("CAP").

17. At the time I became Venture Head, based on my review of ABT-773 documents and discussions with members of the ABT-773 team, as discussed above, and based on my experience in the industry, I was optimistic in April 2001 about the prospects for the compound, although I recognized that, as with all drugs, there would be challenges, both known and unknown, in bringing the compound to market.

ABT-773: Learnings Regarding Potential QT Prolongation and Liver Toxicity Issues as of April 2001

18. When I became Head of the Anti-Infective Venture in April 2001, I was aware from my review of the documents of issues that would need to be addressed during the development of ABT-773. These issues included the potential for liver toxicity and the potential for QT interval prolongation (which can sometimes be associated with arrhythmias). I was aware that both issues would be examined by the FDA for any antibiotic under development. As noted above, by that time I had reviewed the Abbott's end of Phase II data regarding the Phase II studies that had been completed as of the end of 2000. I had also reviewed Abbott's contact report regarding the November 27, 2000 End of Phase II meeting with the FDA, as well as internal memoranda referencing the FDA's focus in general on possible safety issues. Based on my experience in the industry, at the time I became venture head I understood that the FDA and other agencies were going to expect Abbott to supply adequate data to establish that ABT-773 would be safe and effective for use in the patient populations we intended to treat; as the FDA would expect for any drug in development. I further understood that there was a general FDA concern as to whether ketolides (derived from macrolides), such as ABT-773, would have an effect similar to or greater than macrolides with respect to there being a class effect on QT intervals or on liver toxicity. However, none of the information I had learned about ABT-773 itself caused me to doubt that the drug was likely to have a positive benefit-to-risk ratio, given that there was no data that I had seen that led me to believe that there was a specific disqualifying safety issue, either on the part of Abbott or the FDA. In other words, I did not believe at the time I became venture head that the

regulatory challenges faced by ABT-773 were any more significant than the regulatory challenges faced by any other drug of a new antibiotic class.

19. Based on my discussions with Abbott employees and my review of Abbott documents, including two white papers prepared by Abbott's clinical team, including medical directors, for the End of Phase II meeting with the FDA, I understood as of the time I became venture head in or around early April 2001 that Abbott's clinical team did not believe ABT-773 had any QT prolongation or hepatotoxicity issues that could reasonably be expected to have a material adverse effect on the ABT-773 program.

20. I was aware when I became Head of the Anti-Infective Venture that the FDA had raised concerns regarding liver toxicity issues in general. In fact, I learned during the period before I became Venture Head, from reading an ABT-773 Update dated February 12, 2001 provided to me by Dr. Sun, that the FDA had a meeting on guidance to the industry on how to study the potential for liver toxicity in mid-February 2001.

21. I therefore understood when I became Head of the Anti-Infective Venture that Abbott would have to show the FDA that ABT-773 would be safe with regard to not causing liver abnormalities that were unacceptable with respect to extent or severity. I also understood from the documents I had reviewed and my discussions with the ABT-773 team that Abbott had provided information to the FDA regarding liver function issues. However, I had not seen any data in the spring of 2001 that suggested that there was any specific concern at Abbott or from the FDA about ABT-773 itself with regard to liver issues and. In addition, I was aware that the fact that other antibiotics, in particular macrolides, had demonstrated some liver toxicity issues but had not been removed from the market.

22. At or around the time I became Head of the Anti-Infective Venture, I learned that Abbott had observed some evidence of possible liver toxicity among Japanese patients in an early study of ABT-773 conducted in Hawaii. I was also aware from my review of documents and discussions with ABT-773 team members that Abbott had repeated the study and similar results were not seen in that or any other study. D's Exhibit 608 at ABBT205044. A true and correct copy of the February 12, 2001 ABT-773 Update Presentation is attached hereto as D's Exhibit 607 and also reflects that conclusion at ABBT205064. Accordingly, the program under my direction would continue to monitor liver function toxicity data in Phase III clinical studies, but as of the time I became venture head, I had concluded, consistent with what I had been informed by the ABT-773 team, that there was no evidence from the clinical program to date to suggest that there were any issues for ABT-773 with regard to liver toxicity that would jeopardize approval. I recognized that further study would be required on this issue during Phase III.

23. As I discussed above, at the time I became Head of the Anti-Infective Venture, I was aware the FDA had raised general concerns regarding QT prolongation issues regarding all antibiotics, including macrolides and ketolides. I had noted that this general FDA concern was reflected in some of the documents I had reviewed. For example, the ABT-773 Update dated February 12, 2001 that Dr. Sun had provided to me in February, noted that "[t]he potential for QT prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide." D's Exhibit 608 at ABBT205042. There was thus an external environment in which QT prolongation was a general regulatory concern at the time for all drugs, not specifically for ABT-773. I was aware of, and the team discussed the fact that QT prolongation was a general drug safety issue



that needed to be studied in preclinical and clinical trials for antibiotics and, more generally, all pharmaceutical compounds. I was also aware that Abbott would need to provide sufficient data to the FDA to establish the safety of ABT-773 with regard to QT prolongation and to continue to monitor ABT-773 for QT prolongation. In other words, as with all drugs, there was an expectation that we would have to do due diligence, including further studies, to show the FDA that there were no disqualifying safety issues, including QT prolongation problems, with ABT-773.

24. At the time I became Head of the Anti-Infective Venture in April 2001, based on the information provided to me by the responsible ABT-773 team members and by Dr. Sun, I understood that no significant QT issue had been identified for ABT-773 that raised a concern for the future of the compound, despite my understanding that some data indicated that QT prolongation had been experienced with superphysiological doses of ABT-773, doses that far exceeded the therapeutic doses that Abbott was considering for the compound. As set forth in the ABT-773 Update Presentation of February 12, 2001, “no consistent QT effect was observed at clinical doses studied in the Phase IIb studies.” D’s Exhibit 608 at ABBT205061. Similarly, an ABT-773 update presentation prepared by the ABT-773 program, dated March 19, 2001, which I reviewed in the ordinary course of business at or around the time I became head of the program, summarized Abbott’s knowledge of the QT prolongation question as it applied to humans as follows: “Possible dose effect in Phase I at daily dose > 800 mg; No significant QT effect in ketoconazole interaction study; No clinically relevant QT effect in Phase III studies 150 -- 600 mg daily. . . .” Attached hereto as D’s Exhibit 631 is a true and correct copy of this March 19, 2001 update presentation (see p. ABBT120480). In sum, I was not aware of any

evidence as of the time I became venture head in April 2001 that the FDA had any reason to believe that it should have a specific concern about ABT-773 or that Abbott had such a concern. Nor did I believe that anything related to QT prolongation would even delay, much less prevent, the successful launch of ABT-773.

25. Based on my experience in the industry and the information provided to me by my colleagues, I was aware when I became venture head that such successful macrolide antibiotics as clarithromycin had a QT prolongation effect, but this effect was within generally acceptable parameters for an antibiotic used for community-acquired diseases. Accordingly, even if ABT-773 had experienced QT issues, that would not have led me to believe that ABT-773 could not win regulatory approval or experience commercial success. Rather, I understood that ABT-773 would need to demonstrate a safety profile with respect to QT prolongation similar to clarithromycin, assuming at least a similar efficacy profile.

26. In or around April 2001, I was aware as a result of my review of documents and discussions with Abbott employees that the FDA had previously asked Abbott in December 2000 to undertake a two-week dog toxicology study focused on QT and liver toxicity issues. Based on discussions with Abbott's Regulatory Affairs group, it is not unusual for the FDA to call for a variety of incremental studies, particularly preclinical studies such as this dog toxicology study, as the FDA begins to evaluate the data presented to it. I did not regard the request for the dog toxicology study as either unusual or as raising any significant concern for the development of ABT-773. My view of the request for the additional dog study proved correct: By May 2001 the ABT-773 program was able to report to senior management in the program's monthly status report at

ABBT0000510 that this “[a]cute tox study in dog showed no difference from the earlier sedated dog study,” which had had satisfactory results. Attached hereto as D’s Exhibit 638 is a true and correct copy of the May 2001 monthly status report.

27. I was aware in or around April 2001 that members of the scientific community and the pharmaceutical industry were engaged in a vigorous debate about the best ways to read and accumulate QT prolongation data and that new technology was beginning to allow such data to be collected electronically, eliminating certain human errors.

28. At my direction and under my supervision, the ABT-773 program undertook two major efforts to confirm the quality of the assessment of the QT prolongation data and the program’s conclusion that QT prolongation was not an issue for ABT-773. First, the program re-read every single ECG collected in the entire ABT-773 program, using the best available method and under the supervision of a leading expert in the field. Second, Abbott conducted a large, very rigorous clinical trial in which thousands of ECGs were collected using the best available technology. These two efforts confirmed that there was no QT prolongation signal for ABT-773 significant enough to impede regulatory approval.

29. Abbott continued to study the potential for QT and liver toxicity issues, along with many other issues, during the ABT-773 clinical program that went forward after I became Head of the Ant-Infective Venture. These issues, along with all of the other issues that face drug development compounds, continue to be evaluated until the drug is submitted for approval. As I discussed above, however, I did not have any significant concerns that any QT or liver toxicity questions would negatively affect the development of the compound.

ABT-773: Status of Dosing Decisions (QD or BID) For Four Indications as of April 2001

30. When I became Head of the Anti-Infective Venture in April 2001, I was aware that the ABT-773 adult oral formulation program was working to determine the proper dosing, QD (once-a-day) or BID (twice-a-day) for ABECB, pharyngitis, CAP, and ABS, the four indications for which adult oral formulation of ABT-773 was being developed. I was also aware from my review of documents and my discussions with ABT-773 team members that the most valuable market for ABT-773 was in the two less severe indications, ABECB and pharyngitis, which account for approximately 80% of the global respiratory anti-infective market. I recognized that that Abbott's commercial group, in line with market trends, would prefer to have all indications at QD dosing. However, I did not believe that twice-a-day ("BID") dosing for the more severe indications would prove a significant commercial challenge because many of the drugs on the market for those indications were twice-a-day (BID) or three-times-a-day ("TID"). Moreover, although I understood that the commercial team believed once-a-day dosing was preferable (though not an absolute requirement) for the US market, based on my experience in the industry and the information made available to me by the ABT-773 team, I also understood it was less of an issue in markets outside the United States, which were expected to account for a little less than half of the total sales of ABT-773. In fact, I understood that in some parts of the world, such as Japan, it might be seen as preferable to have a more frequent dosing.

31. In or around the time I became venture head in April 2001, I understood from reviewing ABT-773 data and my discussions with responsible members of the ABT-773 team, that we expected that the dosing for the two less severe indications, ABECB and

pharyngitis, would be 150mg QD, that it was uncertain as to whether the dosing for CAP and ABS would be QD or BID, and that the decision with regard to the frequency of dosing for the two more severe indications would be made in the second quarter 2001, after ongoing clinical dose-ranging studies were completed. In other words, we had not yet decided on the dosing level for CAP or ABS and I personally did not know whether CAP and ABS would be dosed at QD or BID in April 2001, because we didn't know what the data from the ongoing dose ranging trials was going to show. Once we had received that data, there would be a decision analysis conducted in order to make the dosing decision regarding CAP and ABS.

32. I reached my understanding of the ABT-773 dosing issues in or around April 2001 from, for example, the Abbott documents that were provided to me in that time frame and which I reviewed at that time. Thus, Abbott's December 5, 2000 portfolio review indicates that as of December 2000, Abbott's Phase II clinical data supported once-a-day dosing for the two less severe (and more commercially significant) indications and the possibility of either once-a-day or twice a day dosing for the two more severe indications. D's Exhibit 608 at ABBT205114. Similarly, the ABT-773 Update dated February 12, 2001 states that "Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD," that "150 mg QD currently being evaluated in ongoing Phase III trials in these indications," that additional dose ranging trials were ongoing for CAP and sinusitis, since there was as yet insufficient data to make a dosing decision as to those indications, and that "[a] decision of 150 mg 'QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01.'" D's Exhibit 608 at ABBT205069-70. Abbott's March 2001 internal monthly status project report for ABT-773 also

projects a “High” probability of achieving once a day dosing for the two less severe indications. D’s Exhibit 613 at ABBT0000429.

ABT-773: Status of Pediatric Program as of April 2001 and Plans for Further Development in Following Months

33. Based on the information provided to me by Dr. Sun and members of the ABT-773 team and on the data I reviewed when I became venture head, I understood in and around the time I became Head of the Anti-Infective Venture that the ABT-773 pediatric oral suspension program was on hold, but that a prototype formulation had been created, certain studies had been completed, and others were planned. This work was reported in the ABT-773 Portfolio Review presentation dated December 5, 2000, which Dr. Sun provided to me in February 2001, and which I reviewed at the time. D’s Exhibit 608 at ABBT205236-205248. In the ABT-773 Update of February 12, 2001, which Dr. Sun also provided to me in February 2001, and which I also reviewed at that time, the program reported that the “[t]he first prototype [pediatric formulation] tested had a taste that was better than clarithromycin,” although “not as good as azithromycin,” and that, while the pediatric program was currently “on hold,” Abbott planned in the future to “reevaluate possible ways of overcoming the taste problem.” D’s Exhibit 608 at ABBT205046. Thus, based on this information and discussion I had with team members in and around the time I became venture head, I understood in April 2001 that, although there were taste issues with regard to the bitterness of the formulation, the program would be moving forward under my direction by doing further work on the pediatric formulation.

34. Although the pediatric program was temporarily on hold and not funded for calendar year 2001, I and the ABT-773 program team did not consider this situation a

matter of concern. Under my supervision, in May 2001 the ABT-773 team completed an assessment of the pediatric development to date and developed a proposal to move forward with further formulation development and Phase I studies, with a view toward finalizing this proposal by July 31, 2001 and presenting it to senior management. D's Exhibit 638 at ABBT0000509 notes this effort. As discussed above, it was my custom and practice in the ordinary course of business as Head of the Anti-Infective Venture to review and approve this monthly status report before it was finalized. This ABT-773 team proposal regarding the pediatric formulation, as well as the fact that Abbott projected spending \$9 million on the ABT-773 pediatric program in 2002 and \$21.5 million in 2003, was in fact discussed at a ABT-773 Decision Analysis Core Team meeting on or around July 25, 2001, which, as I recall, I attended. I also participated in preparing and reviewed and approved the accuracy of the presentation that was made at this meeting, a true and correct copy of which is attached hereto as D's Exhibit FT (see especially pp. ABBT103235.UR - ABBT103239.UR and ABBT103224.UR). Consistent with this Decision Group Analysis and the plans the program had developed under my supervision for the pediatric formulation, in the July 2001 ABT-773 Monthly Status Report, the program reported to senior management that "[a]n assessment of the Pediatric program to-date was completed, and a proposal to move forward with further formulation development and Phase I studies has been developed. FDA guidelines for a pediatric formulation require companies to show due diligence with a pediatric development program. A pediatric proposal will be made to senior management." Consistent with my custom and practice, as discussed above, I would have reviewed and approved this monthly status report in the ordinary course of business before it was finalized. Attached

hereto as D's Exhibit 654 is a true and correct copy of the July 2001 MSPR referenced above (see ABBT0000590). By September 2001, we believed that formulation work on the pediatric program could begin in mid-October and that Abbott would be able to do the first clinical study six months after that date. This expectation is discussed in an email that I received in the ordinary course of business on or about September 20, 2001. Attached hereto as D's Exhibit AL a true and correct copy of that email (see pg. ABBT203480).

35. During the time that I was Head of the Anti-Infective Venture, I was not concerned that the status of the pediatric program would prevent or delay the launch of ABT-773. Based on my discussions with Abbott's Regulatory Affairs team, I understood that the FDA required only that Abbott be conducting pediatric studies at some time prior to regulatory approval of the adult formulation. It was my further understanding Abbott would not be prejudiced in its ability to obtain FDA approval of an adult formulation if its pediatric program was not completed at the time it sought that approval. Moreover, based on my experience in the industry, it is my understanding that the ABT-773 program's planned timing for the development of the pediatric formulation after that of the adult formulation was not at all unusual, given the fact that it is generally considered unacceptable to test products in children until after the products have demonstrated an acceptable level of safety in adults.

The Impact of the FDA's Ketek Advisory on the ABT-773 Program

36. The regulatory hurdle with regard to ABT-773 changed dramatically in late April 2001. On April 26, 2001, the FDA held its first advisory committee meeting for Ketek, a ketolide that was under development by another pharmaceutical company, Aventis, and



was at a more advanced stage of development than any other ketolide. I watched this Ketek advisory together with members of the ABT-773 development team via satellite at Abbott Park. At this meeting, the FDA Advisory Committee voted against approval of Ketek for AECSB and ABS, did not address pharyngitis, and stated that Ketek needed additional data on QT prolongation and liver toxicity prior to approval for CAP.

Attached hereto as D's Exhibit AC is a true and correct copy of an April 27, 2001 email from Jeanne Fox to me, and others, forwarding an April 27, 2001 Health News Daily Article regarding the Ketek Advisory.

37. The April 26, 2001 Ketek advisory was unexpected in a variety of ways. First, prior to the advisory, we believed that Ketek would receive regulatory approval. In the ABT-773 Portfolio Review presentation dated December 5, 2000, which Dr. Sun provided to me in February 2001, the program stated "Ketek . . . will be first-to-market ketolide . . . **FDA advisory 1/29**. . . Expected approval 1Q01." D's Exhibit 608 at ABBT205118 (emphasis in original).

38. The second unexpected (and even more important) aspect of the Ketek advisory related to the focus of the Advisory Committee's concerns. Based on the information that had been provided to me before and shortly after the time I became venture head, I understood from information provided to me by the ABT-773 team that Abbott had expected the focus of the Ketek advisory to be "related to concerns about efficacy and not related to QTc concerns," as discussed in the ABT-773 Update February 12, 2001 that had been provided to me by Dr. Sun in February 2001. D's Exhibit 608 at ABBT205043. In fact, however, the Ketek advisory focused both on efficacy and on the size of Ketek's

safety database, as the April 27, 2001 Health News Daily Article attached to Jeanne Fox's April 27, 2001 email made clear. D's Exhibit AC.

39. Prior to the Ketek advisory, there was no clear direction as to the required size of the safety database for community antibiotics, but based on prior experience it was thought to be about 4,000 patients exposed to the drug. It was also unclear what number of isolates would be necessary to establish a resistance claim, an issue which also directly implicated the size of clinical trials. For example, in the January 2001 MPSR, the ABT-773 program stated that "FDA feedback" regarding a resistance claim was only that a undefined "sufficient body of evidence" needed to be gathered to convince the FDA to grant a claim, and that "they estimate >10 resistance isolates will be required". Attached hereto as D's Exhibit 587 is a true and correct copy of that document. On the basis of our knowledge about the regulatory requirements prior to the Ketek advisory, the program under my supervision, planned for a safety database for its QD testing of 4200 patients, a CAP database (for the resistance claim) of 1000 patients, and estimated 17 isolates. Based on all the information available to us prior to the Ketek advisory, we assumed these plans would be sufficient. This assumption was incorrect, as was shown by the Ketek advisory.

40. The Ketek advisory "raised the bar" for the development of ABT-773 significantly by making it clear that the FDA would in the future require more isolates and therefore greatly increased numbers of patients in clinical trials to prove up a resistance claim, if the claim was achievable at all. Moreover, although it had been known before the Ketek advisory that the FDA was very interested in QT prolongation issues with regard to antibiotics, the fact that Ketek, the first in class drug under review,

was deemed to have issues placed an additional burden on all other drugs in the class being reviewed, including ABT-773, with regard to demonstrating safety. It was only with the Ketek advisory that it became apparent how much the FDA would focus on QT prolongation and what type of evidence would be required. For this reason further data would be required, even if, as was the case with ABT-773, there was no existing evidence indicating that the compound itself had QT issues. With regard to liver toxicity, the impact on Abbott and other drug companies of the Ketek advisory was similarly dramatic. For example, the Ketek advisory revealed that Aventis would be required to perform a 20,000 patient study for liver toxicity because of only two specific cases of liver toxicity that had occurred in the Ketek database. This newly expanded study was expected to cost Aventis tens of millions of dollars and last several years.

41. In the wake of the Ketek advisory, the ABT-773 team, under my direction and supervision, analyzed its implications for us and made presentations to senior management setting forth our conclusions. I contributed to the preparation of some of the slides used in these presentations, and reviewed and concurred with the information set forth in the presentations as a whole. I participated in the actual presentations made to senior management of these materials. For example, attached hereto as D's Exhibit 649 is a true and correct copy of an email from Carol Meyer to me and others dated June 20, 2001, attaching one iteration of such a presentation. Reflecting the ABT-773 program's conclusion as to the importance of the Ketek advisory, the "headline" for the slide beginning the discussion of the Ketek advisory in this presentation is "The Ketek advisory raised the hurdle for the approval of ketolides," and the slide goes on to note that the FDA advisory committee had found "Ketek's 3700 patient safety database

insufficient”. The slide also notes that the FDA had found the number and cure rates for Ketek’s resistance claim isolates insufficient. *Id.* at ABBT229437. The next slide in this presentation spells out the implications that the Ketek advisory had for Abbott’s safety database. Specifically, for the QD outcome, this presentation estimated that the safety database needed to be increased from 4200 to 5000, the CAP patients from 1000 to 1500, and the estimated number of resistance isolates from 17 to 25. Each of these increases, as well as those for the BID outcome databases, meant many millions of dollars in increased costs for the program. An ABT-773 Decision Analysis Core Team presentation, dated July 23, 2001, which I also helped prepare and present on July 25, 2001, sets forth similar conclusions as to the importance and impact of the Ketek advisory, stating that the “Ketek advisory defined new regulatory standards,” and “influences program size”. D’s Exhibit FT.

42. D’s Exhibit EC is a December 2001 ABT-773 presentation to senior management reflects that after further analysis of the Ketek advisory we had concluded that we would have to add still more patients to the safety database, requiring greater additional expenditures and even more time than we had originally calculated. Attached hereto as D’s Exhibit EC is a true and correct copy of the December 2001 “ABT-773 Agenda” presentation (see pp. ABBT271786-87).

43. In sum, the information we had received from the Ketek advisory, and our analysis of its implications, led us to conclude that the Ketek advisory was a watershed for the ABT-773 program, not because of any specific concerns about ABT-773 itself, but because of the increased stringency of the regulatory environment, likely for all antibiotics but for ketolides in particular. This increased stringency, only made apparent

by the Ketek advisory, meant that Abbott would have to re-think the size and adequacy of our safety database and evidence and also the number of isolates that would be required to establish a resistance claim. I and others at Abbott concluded that the Ketek advisory meant that the ABT-773 program would have to incur much greater expense and take much longer to complete than we had had anticipated prior to April 26, 2001 if we hoped to satisfy the FDA's requirements. These conclusions are reflected in summary of the status of ABT-773 in an "Operations Highlights" presentation for a September 7, 2001 Board of Directors meeting. Attached hereto as D's Exhibit 501 is a true and correct copy of this presentation. Specifically, this presentation states, "Based upon experience gained from . . . Ketek FDA advisory meeting, the size of ABT-773 (Ketolide antibiotic) safety database has been increased. This will result in a one year delay in the filing of ABT-773." I provided input to this portion of the presentation and agree with its contents, based on my experience and knowledge of the ABT-773 program at the time.

Post-Ketek Advisory Events Negatively Affecting the ABT-773 Program

44. As discussed above, as of March and April 2001, we were evaluating whether to continue to pursue once-a-day dosing for the two more severe indications, CAP and sinusitis, or pursue twice-a-day dosing. We were planning to base this decision on our analysis of the clinical data that would be released in the summer of 2001. By July 2001, after we had analyzed the Ketek advisory, the clinical data was not yet available, and we faced the decision of whether to wait for the release and analysis of the data, and lose time on the path to regulatory approval, which we now believed in light of Ketek would in any event take longer than we had previously estimated, or make a decision based on the available data. In order to minimize risk and avoid delays on the path to regulatory

approval, we decided to pursue twice-a-day dosing for the launch of CAP and sinusitis. This decision is reflected in D's Exhibit FT, the July 23, 2001 ABT-773 Decision Analysis Core Team presentation discussed above, at ABBT103208.UR, where the presentation notes that the "expected value of selecting the BID dosing" for CAP and sinusitis exceeded the "value of waiting for the dose-ranging data" from clinical studies that were still ongoing. This was not an irrevocable decision, however. As reflected in the ABT-773 July 2001 status report, we planned to continue to evaluate options to achieve once-a-day dosing for those indications, and to attempt to develop an effective once-a-day dose for them after the initial launch. D's Exhibit 654 at ABBT0000589. In addition, we continued to plan a program by which we would be able to offer once-a-day dosing for the less severe indications. *Id.*

45. In November 2001, the results of a critical pharyngitis trial indicated that ABT-773 at the QD 150mg dose would not demonstrate sufficient efficacy for that indication. The loss of this indication, one of the larger indications for which ABT-773 adult oral formulation was being developed, had extremely negative implications for the potential value of ABT-773. In a January 7, 2002 memorandum regarding the status of ABT-773 that Dr. Sun and I prepared based on information for ABT-773 team members and sent to Miles White, Abbott's CEO, we stated that "[t]he loss of the pharyngitis indication is forecasted to erode more than \$117 million in NPV from ABT-773 . . . ." Attached hereto as D's Exhibit 673 is a true and correct copy of this memorandum (see pg. ABBT207775). In the presentation to Mr. White regarding ABT-773 that I prepared and made in January 2002, a true and correct copy of which is attached hereto as D's Exhibit 676, I similarly emphasized the negative impact on the program resulting from the failure

of the pharyngitis indication. *Id.* at ABBT220672 (indicating a loss of \$117 million due to pharyngitis) and ABBT220666 (“By losing the pharyngitis indication, ABT-773 is left to compete in 53% of the adult global respiratory anti-infective market.”). To the best of my knowledge, based on my knowledge of and experience with ABT-773, the information included in the January 2002 memorandum and presentation was true and accurate. I understood at the time I participated in the preparation of these documents that they would be relied upon by Abbott’s senior management in making decisions about the ABT-773 program.

46. As I set forth in the above-referenced January 2002 presentation and memorandum to Mr. White, there were several events that had occurred after April 2001 that had a profound negative impact on the ABT-773 program and caused the members of the ABT-773 to have much greater concern about the future of ABT-773 than the team and Abbott generally had had prior to April 2001. First, as I explained in the January 7, 2002 memorandum to Mr. White, the Ketek advisory demonstrated an environment of “[i]ncreasing regulatory stringency” and meant that “the projected size of the required safety database for ABT-773 has increased considerably [as a result of the Ketek advisory]. This will increase the expense and duration of the phase III trials.” D’s Exhibit 673 at ABBT207774. Second, I noted that the Ketek advisory made clear that a resistance claim for ABT-773 would require a “larger number of resistant isolates” and that, like the need for a larger safety database also established by the Ketek advisory, “this requirement will significantly increase the size, complexity, and duration of clinical trials”. *Id.* Third, I emphasized that “the loss of the pharyngitis indication (as demonstrated by late 2001 clinical trial results) is forecasted to erode more than \$117

MM in NPV from ABT-773.” *Id.* at ABBT207775. Fourth, I explained that in July 2001 the program had determined, in light of the increasingly stringent regulatory environment evidenced by the Ketek advisory and other information developed since April 2001, had chosen “twice daily dosing . . . for the pivotal Phase III clinical trials in sinusitis and community acquired pneumonia. This decision was taken based on accumulated scientific data and to enhance regulatory approvability of the compound, but recognizing a corresponding decrease in the commercial value. . . .” *Id.* at ABBT207773. Fifth, I noted that “liver enzyme elevations had been observed in a few subjects in clinical trials, most recently in a study to evaluate QT prolongation.” *Id.* at 207775. The recent trial to which we referred in this memorandum was the Abbott M01-325 clinical trial, which began on October 3, 2001, and which was put on hold due to unexpected liver elevations seen in four patients. As we stated in the January 2002 memorandum to Mr. White, “Although the incidence and severity of these findings fall within an acceptable range for antibiotics, further findings may drive the requirement for a larger safety database”. *Id.* In other words, we were concerned, after the Ketek advisory, that any clinical trial safety data that implicated safety concerns, even if that data was within an acceptable range for antibiotics, could result in an FDA requirement of a greatly enlarged safety database and cause Abbott to incur much greater development costs than it had expected prior to April 26, 2001, to prove that ABT-773 was safe. The safety issues referenced in the January memorandum to Mr. White were significant only in light of the fact that April 2001 Ketek advisory had significantly raised the hurdle for establishing safety for the class of drug to which ABT-773 belonged. D’s Exhibit 676 at ABBT220671 (“Complete analysis of liver function tests of entire database revealed no significant case of liver toxicity.



However, a finding of a single case in the future could drive database requirement of up to 10,000 patients.”).

47. In slide 1 of the January 2002 presentation, which I gave to Mr. White, I summarized the most important information that we had learned about ABT-773 since before the Ketek advisory in April 2001 as follows:

Since the April PEC, the development plan has been impacted by:

The Ketek (Aventis) advisory defined the minimum safety and resistance databases for Ketolide anti-infectives

The BID dosing at variance with market trend to short course once daily therapy

Loss of pharyngitis indication impacts program financially and has regulatory impact

The drug is still technically approvable with cost and time penalties, but commercial attractiveness has decreased substantially.

D’s Exhibit 676 at ABBT220665.

Each of these issues was based on developments that occurred after March 2001, when I understood the agreement between Hancock and Abbott was entered into.

Abbott’s December 10, 2001 Decision to Place the ABT-773 Program on Hold and Mid-2002 Decision to Terminate Development of ABT-773 and Out License the Compound

48. On December 10, 2001, the PEC met to review the development status of ABT-773. At that meeting, I presented the information that the program had received about ABT-773 and the regulatory environment since mid-April 2001. Based on the data it reviewed at that meeting, the PEC put the ABT-773 program on hold, although existing studies were to be completed. In addition, as set forth in the January 7, 2002 memorandum from Dr. Sun and myself discussed in detail above, the PEC also

recommended to Mr. White that Abbott suspend further development of ABT-773 and initiate efforts to out license the compound. D's Exhibit 673 at ABBT207773.

49. I attended a meeting with Mr. White in January 2002 in which I made a presentation setting forth the basis for the PEC's recommendation to suspend further development. Mr. White did not announce any decision about the future of ABT-773 at that time. We completed the existing clinical studies through the first half of 2002. However, no new studies were started. In February 2002, we informed our employees that there was a delay in the development timeline of ABT-773. Towards the middle of 2002, Dr. John Leonard informed me to fully suspend development of ABT-773 and work with the licensing group to explore the out licensing of the compound.

Abbott's Out Licensing of ABT-773 to ALS

50. I was actively involved in Abbott's efforts to out-license ABT-773 after the decision had been made that Abbott would discontinue its development of the compound. I participated in presentations that Abbott made to potential partners, including Elitra. I was aware that Abbott negotiated a license agreement with Elitra in December 2002. I was also aware that Elitra's funding fell through after several months and it was unable to develop ABT-773. I also participated in meetings with Advanced Life Sciences ("ALS").

51. After Hancock had given its consent, Abbott entered into an ABT-773 licensing agreement with ALS in December 2004. I participated regularly in discussions with ALS regarding the development of the compound and I monitored that development. When I began my work with Astellas, Astellas asked me to discontinue my work with ALS. I continue to monitor the development of the compound through the public announcements

that ALS occasionally makes about it and through information that ALS sends me from time-to-time.

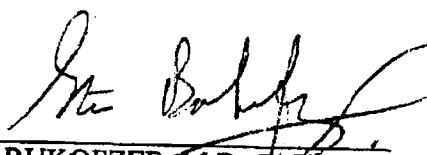
ALS's Development of ABT-773 ("Cethromycin")

52. Based on my participation with regard to ABT-773 on the ALS scientific board review and my review of publicly available sources, I am aware that ABT-773 is currently under development as "cethromycin" by ALS. On June 21, 2007, ALS announced results from its most recent clinical trial. Attached hereto as D's Exhibit 732 is a true and correct copy of the June 25, 2007 Advanced Life Sciences Form 8-K. According to ALS, ABT-773 or cethromycin "achieved positive safety results in the study" and "liver function tests and electrocardiogram monitoring demonstrated no significant differences between subjects receiving cethromycin and subjects receiving Biacin," an antibiotic that is currently on the market today. *Id.*

53. Based on my review of publicly available sources, I am also aware that ALS has publicly announced that: (1) it expects to launch the drug to the public at the end of 2008; (2) it plans to launch with once-a-day dosing; (3) the drug's safety profile is consistent with Biacin, an antibiotic currently on the market; (4) analysts have projected that the compound could achieve peak sales of \$500 million a year; and (5) under the terms of the RFA and the out-licensing agreement that Abbott negotiated, with Hancock's approval, Hancock will receive substantial royalties and milestone payments if ALS successfully launches the drug. See, for example, June 25, 2007 Advanced Life Sciences Form 8-K; Crain's Chicago Business June 29, 2007 Article ("According to Elmer Piros, a New York-based analyst with Rodman & Renshaw LLC, Cethromycin could eventually reach 25 percent of the \$2-billion global market for drugs that fight community-acquired

pneumonia.”); Crain’s Chicago Business June 11, 2007 Article (“If the drug passes its trial, analysts expect FDA approval and a product launch by year-end 2008.”); and Life Sciences Weekly August 21, 2007 Article (ALS “announces positive results” from key cethromycin clinical trial”), true and correct copies of which are attached hereto as D’s Exhibit 732, BU, BS and BX, respectively.

I declare under penalty of perjury, under the laws of the United States of America, that the foregoing is true and correct. Executed this 17 day of February 2008, at Highland Park, Illinois.

  
STANLEY BUKOFZER, M.B., B.Ch., M.  
Med. (Int. Med.)

**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

\_\_\_\_\_/s/ Eric J. Lorenzini  
Eric J. Lorenzini (*pro hac vice*)



# **Operations Highlights**

**September 7, 2001  
Board Meeting**

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## Pharmaceutical Products Division Highlights



- **Anti-Infective** – Continue Biaxin life cycle management  
REDACTED
  - Biaxin XL received FDA approval for Community-Acquired Pneumonia
  - Omnicef co-promotion agreement  
REDACTED
- **Urology/Cardiology** – Increase commercial presence in Cardiology.  
REDACTED
  - Addition of 100 sales representatives to promote TriCor
  - Expansion of Mavik (ACE inhibitor) and Tarka (ACE/Calcium blocker combo)
  - Flomax  
REDACTED



## Pharmaceutical Products Division Highlights



(cont.)

- **HIV** – Focus on the use of Protease Inhibitors in earlier AIDS treatment regimens.
  - Kaletra continues to grow, REDACTED
  - Abbott is now the #1 protease company
- **Diabetes / Metabolism**
  - Submitted the Synthroid NDA to the FDA on August 1, 2001, REDACTED
  - The Direct-to-Consumer advertising used by Knoll for Meridia
- **Immunology** – Establish Abbott as a premier company in rheumatoid arthritis
  - D2E7 development program
  - Pre-marketing activities REDACTED
  - Projected peak year sales of D2E7

## Pharmaceutical Products Division Highlights

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### Operational

- US Knoll integration continues on track with several key milestones achieved.
  - An Immunoscience drug development center of excellence
  - The Mt. Olive headquarters
  - Knoll's business system, SAP,

REDACTED

### R&D

- The clinical development of ABT-627, (Atrasentan) for prostate cancer is continuing on schedule. Two pivotal Phase III trials have recently been initiated.
- Based upon experience gained from HMR's Ketek FDA advisory meeting, the size of ABT-773 (Ketolide antibiotic) safety database has been increased. This will result in a one year delay in the filing of ABT-773.

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January 2001

## ABT-773 Project Status Report

## Monthly Highlights

- We sent responses to the FDA based on their written comments from the end of Phase II meeting on Dec 14<sup>th</sup> and have only received feedback on the CAP protocol. We have implemented all requested changes for the other 3 indications and have IRB approved amendments. We have also re-submitted to European ethics committees and MOHs were required.
- All Phase III U.S. studies are actively enrolling patients. European studies will start enrollment this month, as we have initial approvals in at least one country for each protocol.
- Plans are in place to initiate sites in Central America, So Africa and So America for CAP and ABS for their winter seasons starting in June. This will enable us to continue enrolling once the season in the Northern Hemisphere comes to a close and will help to insure that we obtain sufficient patients to make a dose selection for these 2 indications.
- A decision on funding for the IV formulation is required in February to initiate the first Phase I study by April 2<sup>nd</sup>. This study will enable us to determine the appropriate IV dose and evaluate injection site pain with the formulation prior to a Multiple Dose study. Timing for Phase I Go/No Go by September is critical if we would like to have an IV filing within a year of the tablet filing.
- The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period.

<b>Key Progress Gauges - January Accomplishments</b>		<b>Target Date</b>	<b>Status</b>
Complete End of Phase II CMC/BioPharm package to request meeting with FDA.		01/31	To be completed by 2/16
Complete Phase III protocol amendments and re-submit to European Ethics committees.		01/31	Complete
Complete manufacture of final NDA formulation lots.		01/31	Complete
Make a pediatric strategy recommendation based on team review of pediatric data from formulation, PK, taste evaluations.		01/31	Strategy meeting scheduled for 2/16.
Complete pilot scale activities in IDC for the U.K. manufacturing site.		01/31	Complete
<b>February Projections</b>		<b>Target Date</b>	<b>Status</b>
Initiate enrollment in European Phase III studies.		02/19	
Initiate commercial scale process development for the US formulation.		02/12	
Deliver bulk drug campaigns 14 and 15.		02/16	
Initiate NDA stability of final NDA formulation lots.		02/06	
Submit Phase III comparative CAP & ABS protocols for CRO bids to initiate these studies in 4 <sup>th</sup> Q 2001.		02/28	
Finalize BAL protocol for Japan to initiate in April.		02/28	

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**January 2001**  
**ABT-773 Project Status Report**

**Key Issues/Decisions/Events**

Area	Issue/Decision/Event	Progress
SPD/PARD	A change in bulk drug physical or chemical properties during formulation development will result in a delay in the Aug 2002 filing date. If at the 1200L scale, a delay of up to 18 months.	A strategy for the bulk drug lots that will be used in the NDA formulation runs will be reviewed with the CMC Technical Committee in early December. Bulk drug properties and granulation variables are being evaluated as a means to develop appropriate physical specifications for the bulk drug.
Regulatory	An end of of Phase II meeting with FDA was targeted for the end of September/mid October timeframe, but rescheduled to the end of November at the request of FDA.	Meeting with FDA was held on November 27 <sup>th</sup> . QT effects are the current hot topic for the FDA, and was reflected in the changes they requested to the Phase III program. They also requested an acute tox study in dog to further evaluate cardiac effects. The required "body of evidence" for obtaining a resistance claim for <i>s.pneumo</i> was discussed and the FDA recommendation included having an IV formulation to get bacteremic patients and more serious CAP infections. <b>Protocol amendments have been signed off incorporating all FDA requested changes and implemented in the U.S. and Europe.</b>
Regulatory	Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	FDA concern is whether ketolides behave like macrolides and whether there may be a class effect. They also discussed whether a Phase I study should be conducted in subjects with underlying cardiac disease. ECG monitoring will be done in all Phase III studies with the exception of the ASP study in Europe.
SPD	Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch.	The End of Phase II CMC meeting with FDA will be requested for January 2001 to present the package on starting material definition for step 5 intermediate. Meeting is targeted for the end of March.
Venture/NPD	The pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged.	Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. Phase IIIa studies to be complete by 5/2001 to decide the dose requirements for CAP and ABS. <b>To address this issue and potentially create a new model for evaluating PK/PD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts June-July 2001 to define further study.</b>
NPD	Phase IIIa data will be important predictors of commercial value of compound (QD vs BID dosing for CAP/Sinusitis, efficacy, adverse event rates.	Phase IIIa studies to be complete 5/2001. FDA changes to the Phase III protocols creates a challenge for us to still meet the Go/No Go decision for the QD vs BID dose for CAP and ABS by June. The team is working to overcome the challenges as much as possible.

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**January 2001**  
**ABT-773 Project Status Report**

Area	Issue/Decision/Event	Progress
<b>Venture</b>	Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .	FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required, CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim.
<b>Clinical</b>	The Phase III clinical program is large, intense, and must be conducted successfully in a relatively short period of time.	FDA requested changes are being assessed for protocol amendments. The subject Informed Consent revisions were submitted to central IRBs and approval was obtained by Dec. 8 <sup>th</sup> . <b>No FDA feedback was received on our responses to the End of Phase II meeting for ABS, ABECB or ASP protocols. We have incorporated all requested changes and submitted to IRBs in the U.S. and Ethics Committees/MOHs in Europe. European study enrollments expected to start in mid-February. We are working to start countries in the So Hemisphere to compensate for the delays.</b>
<b>Japan</b>	Due to the dose change in the base development program, Phase I will be repeated in Japan to further evaluate dose-ranging. An increase in liver enzymes was observed in the low and medium dose groups of Japanese volunteers in the first study in Hawaii, and will be further evaluated in the Phase I studies done in Japan. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period. The Japanese BAL study will start in April. Dose selection and BAL results need to be available prior to a meeting with Kiko to discuss the Phase II/III strategy.
<b>HPD</b>	The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Year 2001 funding was committed by HPD.	HPD funding for 2001 (\$7MM) is no longer approved. At the ABT-773 Portfolio meeting, Jeff Leiden committed to find funding (approx. \$1MM) to do the Phase I studies for the IV 2001 to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements. <b>Need confirmation on funding availability in February to initiate Phase I in April.</b>

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**January 2001**  
**ABT-773 Project Status Report**

Project Cost Summary - January					
\$000's Activity	Cumulative through 2000	YTD Actual	Projected Year-end	Current Funded Year-end	Variance
Clinical Program	46.5	6.6	61.7	61.7	...
CMC (PAR, SPD & IDC)	77.9	1.4	21.7	21.7	...
Drug Safety	9.0	.1	1.9	1.9	...
Other Support Costs	20.4	.3	2.7	2.7	...
Total	153.8	8.4	88.0	88.0	...
					Cumulative to NDA
					136.4
					110.5
					11.7
					29.1
					287.7 *

**Tablet NDA = 8/2002; IV Formulation unfunded; Pediatric Formulation unfunded.**

\* Cumulative cost to NDA based on 3Q 2002 filing.

Clinical Study Progress						
Protocol # - Study Name	Start (1 <sup>st</sup> Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients	Current Enrollment	
M99-048, Phase II Dose Ranging, ABECB	9/1/99	3/31/00	3,885	300	384	
M99-053, Phase II Dose Ranging, Sinusitis	9/1/99	4/30/00	3,172	300	292	
M99-054, Phase II Dose Ranging CAP	9/1/99	4/30/00	4,089	300	187	
M00-219 Phase III CAP, Dose Ranging	11/7/00	4/30/01	14,400	800	68	
M00-216 Phase III ABECB vs Azithromycin	11/7/00	4/30/01	7,381	600	125	
M00-217 Phase III ABECB vs Levofloxacin	11/7/00	4/30/01	4,600	500	0	
M00-225 Phase III Sinusitis Dose Ranging	11/7/00	4/30/01	7,200	600	126	
M00-223 Phase III Pharyngitis vs Penicillin 250mg TID	11/7/00	4/30/01	4,340	520	161	
M00-222 Phase III Pharyngitis vs Penicillin 500mg TID	11/7/00	4/30/01	5,000	520	0	

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January 2001

## ABT-773 Project Status Report

**Business Rationale**

Date: January 2001

Acquired

Franchise: Anti-infective

Venture: Anti-infective

ABT #:

ABT-773

Trade &amp; Generic Name:

TBD, TBD

Mechanism of Action:

Ketolide, antimicrobial

Indications: Acute Exacerbations of Chronic Bronchitis, Community

Pneumonia, Pharyngitis, Acute Maxillary Sinusitis

**Product Profile**

Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Activity against Gram +, Gram -, atypicals	3/1997	High	Confirmed	High
Activity against <i>H. influenzae</i> = azi	3/1997	High	Confirmed	High
Active against 80% of Gram + resistant strains of efflux and MLS-c	3/1997	High	Confirmed	High
Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	3/1997	High	Confirmed	High
Incidence of GI side effects=azi	3/1997	Low	Not Met	High
Incidence of drug-interactions = clari, no contraindications	3/1997	High	6/2001	Medium
QD dosing adult/tablet	3/1997	Medium	6/2001	High
QD dosing ped OS	3/1997	Medium	9/2000	Medium
QD dosing for IV	3/1997	Medium	12/2000	High
Comparable pain at injection site than azi	3/1997	Medium	12/2000	Low
Less metallic taste than clari XL	3/1997	Medium	6/2001	High
OS equal in taste to Azi, Omnicef		Low	9/2000	High
5-day therapy for most indications	3/1997	Low	6/2000	High
COGS > 80% SMM at launch	3/1997	High	12/2001	Low
Maintain balanced plasma/tissue levels similar to clari		Medium	12/2001	Medium

\* Probability Key:

High = 70-100%

Medium = 30-69%

Low = 0-29%

**Market Forecast**

	PPCC/DDC 3/1997	Revised 1/1999	Current Revised 8/2000 Tab/Cap Only*
Patent Status:	9/2016	9/2016	9/2016
NDA Filing:	12/2000(tab/cap)	8/2002 (all)	8/2002 (tab/cap)
	9/2001(OS,IV)		
Ex-U.S. Filings:	2/2000(tab/cap)	8/2002 (all)	8/2002 (all)
	9/2001(OS,IV)		
Projected U.S. Launch:	4/2002(tab/cap)	9/2003	8/2003
	1/2003(OS,IV)		
Projected ex-U.S. Launches:	4/2002(tab/cap)	9/2003	8/2003
	1/2003(OS,IV)		
Peak TRx Share, U.S.:	4.4%TC;4.7%OS;	4%TC;4%OS;	7.5%
	3.3%IV	10%IV	
Peak TRx Share, ex-U.S.:	N/A	3.3%TC;N/A OS,IV	4.4 to 6.9%
Peak Sales, U.S.:	\$428TC; \$118OS	\$399TC; \$58OS	\$432
(\$MM)	\$26IV	\$13.8IV	
Peak Sales, ex-U.S.:	N/A	\$360TC;N/A OS,IV	\$386
(\$MM)			
Post-Tax NPV @ 12.5%, U.S.:	N/A	\$200TC; (\$6.1)OS	\$297
(\$MM)		(\$1.1)IV	
(no clari cannibalization)		(note: discount rate was 15%)	
Post-Tax NPV @ 12.5%, ex-U.S.:	N/A	\$240TC;	\$208
(\$MM)		N/A OS, IV	
(no clari cannibalization)		(note: discount rate was 15%)	
Avg daily dose			150mg QD
Target Drug Cost/kg at Launch	\$1163TC; \$2173OS	\$3633TC; \$291OS	\$3000
	\$3720IV	\$8953IV	
SMM at Launch (U.S.,Ex-U.S.)	--	86%TC;63%OS;100%	85%, 87%
SMM at Year 5 (U.S.,Ex-U.S.)	--	IV94%TC;82%OS;58%I	90%, 93%

\* Includes Tab/Cap only. A development plan will be established for OS and IV programs.

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# January 2001 ABT-773 Project Status Report

## Project Overview

Metrics Dates	
Description	Date
DDC Meeting	3/1997
Start of first GLP animal tox study	6/1997
First dose in human (beg. Phase I)	12/1997
First dose in patient (beg. Phase II)	9/1999
First dose in Phase III	11/2000
Last Patient/Last Visit	4/2002
NDA Filing	8/2002
NDA Approval	8/2003
Europe (EMEA) Filing	8/2002
Europe (EMEA) Approval	8/2003
Japan Filing	TBD
Japan Approval	TBD

See the following page for a summary of Bulk Drug deliveries in SPD.

## PARD

Activity	Plan 12/1998	Actual
Phase I Formulation (Caps)*	12/1997	12/1997
Phase II Formulation (Tablet)	7/1999	8/1999
Clinical Supplies Phase IIB	7/1999	8/1999
Phase III Formulation (Tablet)	4/2000	7/2000
Phase III Clinical Supplies Manufactured	9/2000	9/2000
NDA Lots (3) Completed	7/2000	01/2001
Completion of 1 Year Stability for NDA	8/2001	
Formulation Peer Review	11/2001	

## Toxicology

Toxicology Activity	Plan Start 12/1998	Actual Start Date	Report Completed
2-week oral Rat/Monkey	7/1997	6/1997	9/1998
Acute Studies	8/1997	8/1997	12/1997
Mouse Lymphoma/Micronucleus	11/1997	11/1997	4/1998
1 Month Rat/Monkey	12/1997	12/1997	12/1998
Pregnant Rat/Rabbit RF	1/1998	1/1998	11/1998
SEG II Rat/Rabbit	3/1998	3/1998	2/1999
Guinea pig sensitization	11/1998	11/1998	2/1999
3 Month oral Rat/Monkey	9/1999	10/8/1999	8/2000
Seg I/III Rat	9/1999	10/8/1999	12/2000
IV Irritation studies, set 1	7/1999	7/15/1999	8/1999
IV Irritation studies, set 2	2/2000	2/2000	3/2000
IV 2-week Rat/Monkey Studies	6/2000	6/2000	01/2001
Neonatal/Juvenile Rat	10/1999	11/1999	7/2000

January 2001  
ABT-773 Project Status Report

SPD ABT-773 Bulk Drug Deliveries Update

	<u>Target Date</u>	<u>Amount</u>	<u>Delivery Date</u>	<u>Amount</u>	<u>Lot #</u>	<u>Amount after milling</u>
Campaign 1	2/28/99	200 Kg	2/23/99	209 Kg	50-007-CA-00	207.5 Kg (2/26)*
Campaign 2a	6/15/99	140 Kg	6/17/99	131 Kg	54-702-NI-00	129.4 Kg (6/19)*
Campaign 2b	7/15/99	140 Kg	7/21/99	121.5 Kg	55-208-CB-00	119.3 Kg (8/4)*
Tox lot	8/30/99	5 Kg	8/25/99	6.1 Kg	55-718-NI-00	
Campaign 3a	9/30/99	160 Kg	10/8/99	170.5 Kg	58493CB00	138.4 Kg (10/16)*
Campaign 3b	10/21/99	160 Kg	10/11/99	176.5 Kg	58494CB00	169.5 Kg (10/16)*
Pilot run 1	-----	15 Kg	10/30/99	18.9 Kg	59763N100	no milling
Pilot run 2	-----	15 Kg	2/5/00	15.5 Kg	61790NI00	no milling
Pilot run 3	-----	25 Kg	1/30/00	27.5 Kg	62764CB00	27.3 Kg (4/18)*
Campaign 4	12/10/99	320 Kg	11/23/99	355 Kg	61741CB00	309 Kg (3/2)*
Campaign 5	12/30/99	300 kg	12/16/99	300.5 Kg	60665CB00	269.2 Kg (3/3)*
Campaign 6	2/28/00	280 Kg	2/23/00	321 Kg	62796CB00	315.5 Kg (3/6)*
Campaign 6 (IV)	2/28/00	15 Kg	2/22/00	20 Kg	62797CB00	18 Kg (3/15)*
Campaign 7	3/30/00	300 Kg	4/10/00	370 Kg	63890CB00	361.2 Kg (4/18)*
Campaign 7 (IV)	3/30/00	5 Kg	3/29/00	19 Kg	63889CB00	17.2 Kg (4/11)*
Campaign 8	4/25/00	200 Kg	5/11/00	263 Kg	64970CB00	256.5 Kg (5/15)
Campaign 8 (IV)	4/25/00	15 Kg	4/25/00	19.8Kg	64971CB00	17.7 Kg (5/11)*
Campaign 9	6/15/00	300 Kg	6/14/00	375.7 Kg	65064CB00	355.7 Kg (6/20/00)
Campaign 9 (IV)	6/15/00	15 Kg	6/5/00	18.1Kg	65065CB00	16.7 Kg (6/9/00)*
Campaign 10	7/15/00	300 Kg	7/26/00	361.2 Kg	67176CB00	359.0 Kg (8/10/00)
Campaign 11	8/15/00	300 Kg	8/4/00	333.7 Kg	68285CB00	271.9 Kg (9/7/00)
Campaign 12	10/6/00	300 Kg	9/27/00	356 Kg	69458CB00	292.3 Kg (12/8/00)
Campaign 13	11/23/00	300 Kg	11/15/00	351.2 Kg	71665CB00	349.1 Kg (12/20/00)
				Total (year 2000)		2,815.5 Kg

\* Weight after rework

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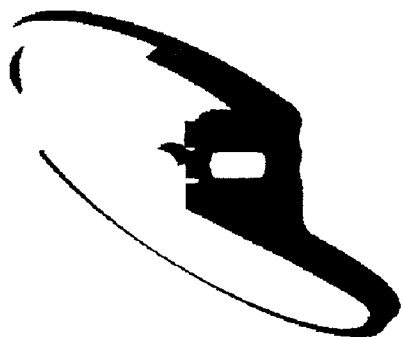
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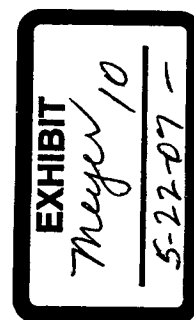
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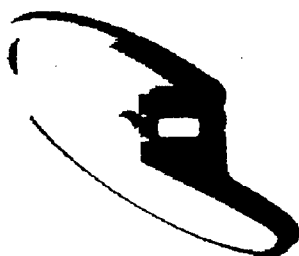


# ABT-773 Update February 12, 2001



# Agenda

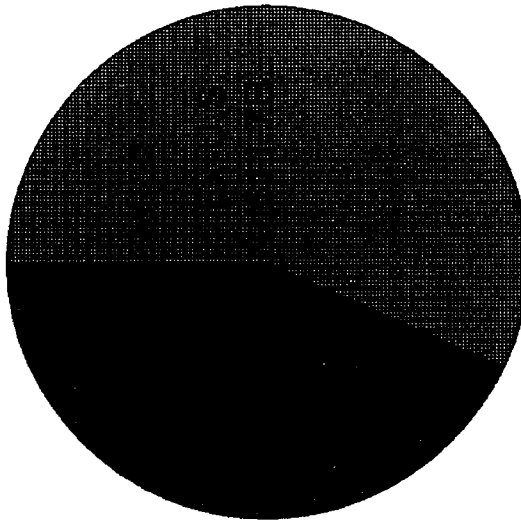
- Introduction
- The molecule
- Phase III tablet program Issues
  - QT
  - Liver Function
  - Dosing
- IV program
- Pediatric program
- Japan program



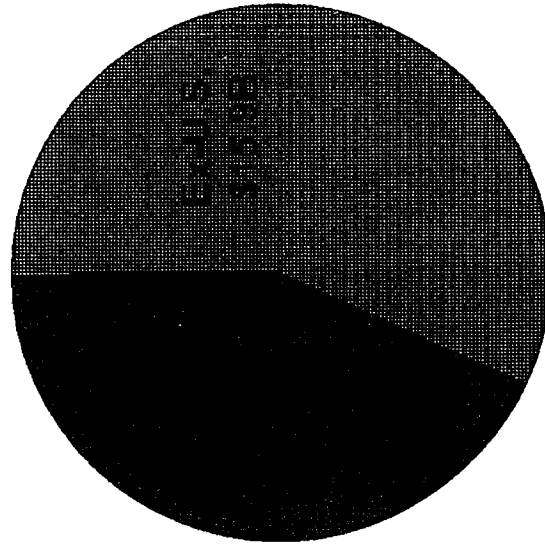


## Global Antibiotic Market Sales Current vs Future Projection

1999 Global Sales \$20.6B



2005 Global Sales \$25.3B



The antibiotic market is a large market and is expected to expand on a global sales basis

# Global Market Drivers

## Negative vs Positive Drivers

### • Antibiotic Resistance

Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓  
Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

### • Patent Expirations

May increase price sensitivity and bargaining power of MCOs ↓  
Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑

### • Unmet Need ↓

–Overall unmet need relatively low  
–Cost, convenience, tolerability take on added importance  
–Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

### • Competition ↓

–6 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox  
–Continued discovery/development activity by key competitors  
–High level of promotional activity

Negative driver ↓  
Positive driver ↑

# Key Success Factors

## U.S. vs ex-U.S.

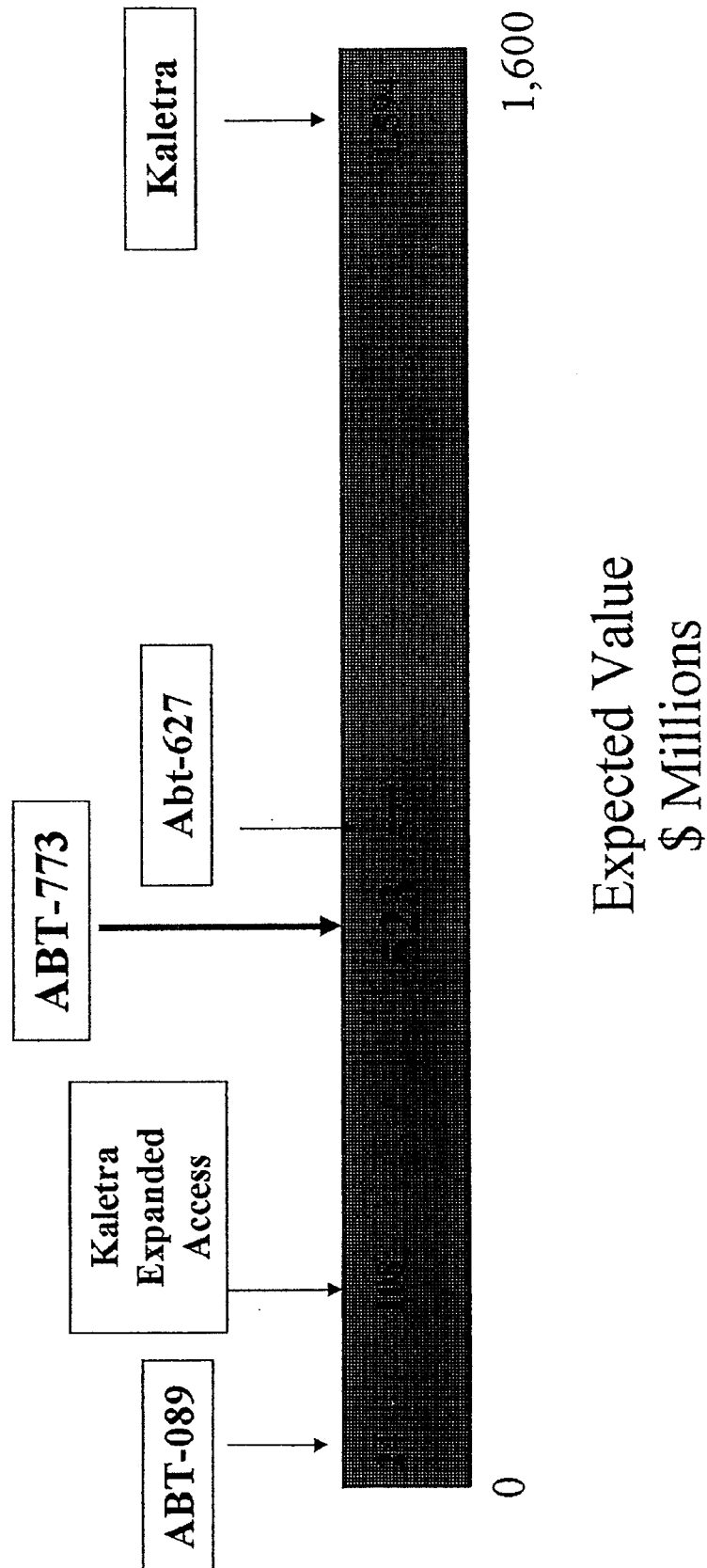
U.S. Assessment			Ex-U.S. Assessment		
Profile	Efficacy	++	Requires a certain baseline level of efficacy across all indications as a "ticket to entry", but is difficult to differentiate agents based on efficacy	+++	While also difficult to differentiate based on efficacy, efficacy takes on added importance with respect to regulatory approval, especially in CAP.
	Tolerability	+++	Success of Zithromax and Levaquin have redefined expectations for tolerability of new agents; agents must offer very good tolerability given numerous alternatives	++	Although important, markets are willing to bear somewhat higher incidence of adverse events, provided they are not severe (i.e. taste perversion); over time, however, AE hurdles will continue to be increased
	Convenience	+++	Zithromax and recent quinolones have moved the market toward short course therapies dosed once daily; Biaxin in 1991 represented the last major BID entrant	++	While in some cases durations are even shorter (azi 3-day AECB), market levies relatively minor penalties for BID dosing
	Resistance Claim	++	Important to leverage the overall ketolide message, and to maximize formulary access, although availability of data may be able to accomplish same end	+++	May prove critical in the regulatory decision of approvability, as well as in setting premium pricing
	Price	+	Able to set price in accordance with optimal price/demand relationship; only moderate price sensitivity in market, though this could increase with increased number of generic competitors over mid-term	+++	Pricing figures heavily into the overall profitability of the compound and is governed by merits of product profile relative to other agents.
Regulatory	Approvability	+	With data showing equivalence to comparators, is not a major area of concern	+++	Will take into consideration PK profile in addition to clinical data, which could weaken argument for approval; given the pivotal nature of CAP approval to overall compound viability, regulatory risk is magnified; will require very strong clinical data if 150-mg OD is to be supported
Profitability	COGS	+	Allows for > 90% SMM given price parity to Zithromax	++	Due to pricing constraints, COGS represents a larger issue; current estimates are 75% SMM at launch rising to 87% peak
	Price	+	Assumes price parity to Zithromax	+++	Profile may limit optimal pricing

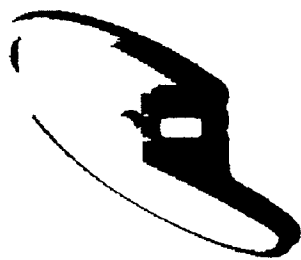
+ Minor Factor

++ Moderate Factor

+++ Major Factor

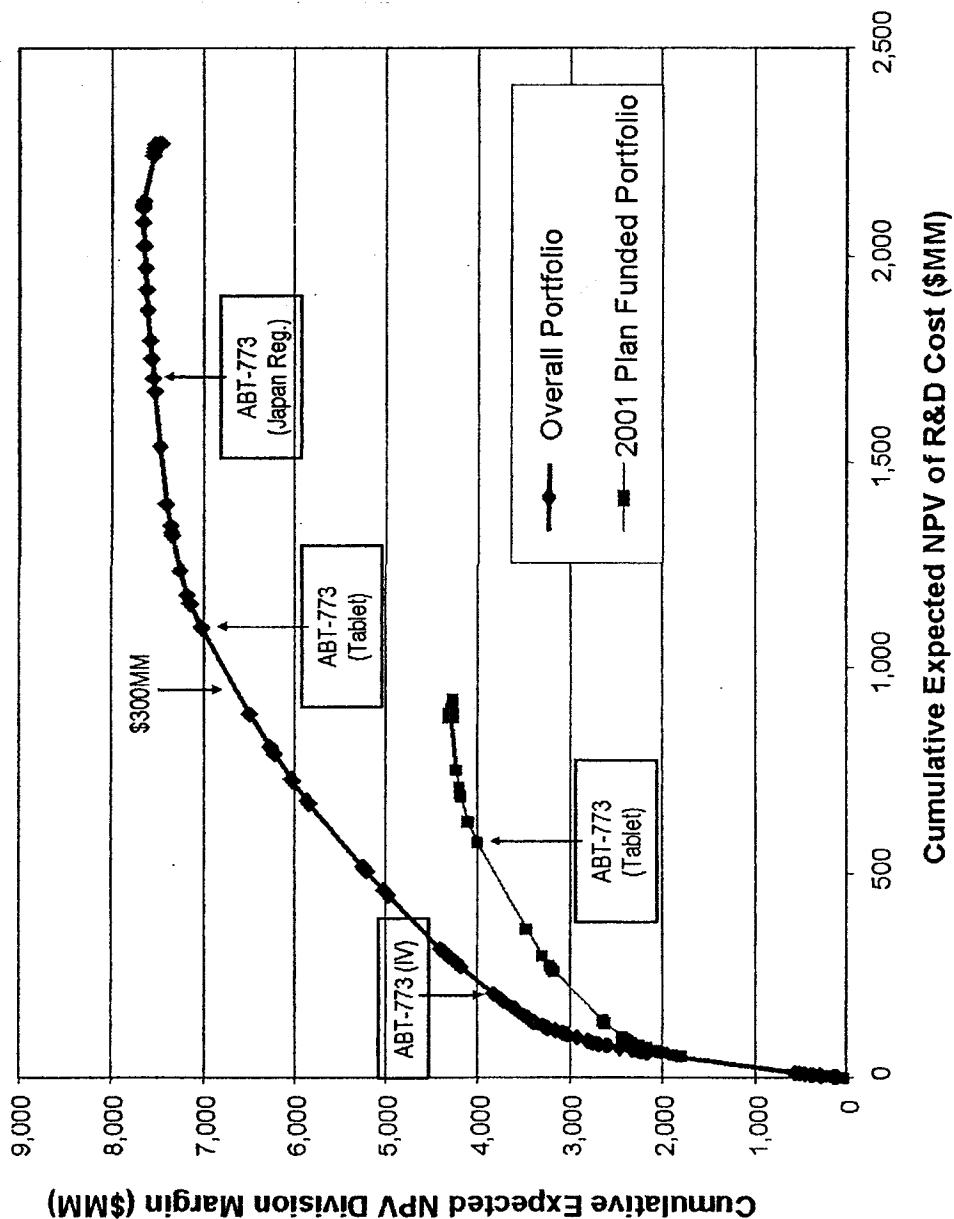
# ***ABT-773 Comparison with other funded projects in 2001 Plan Portfolio***



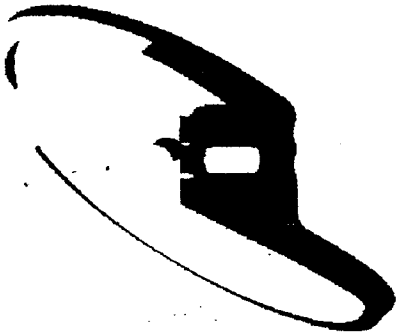


# ***ABT-773 Comparison with other funded projects in 2001 Plan Portfolio***

## **Portfolio Productivity Analysis**



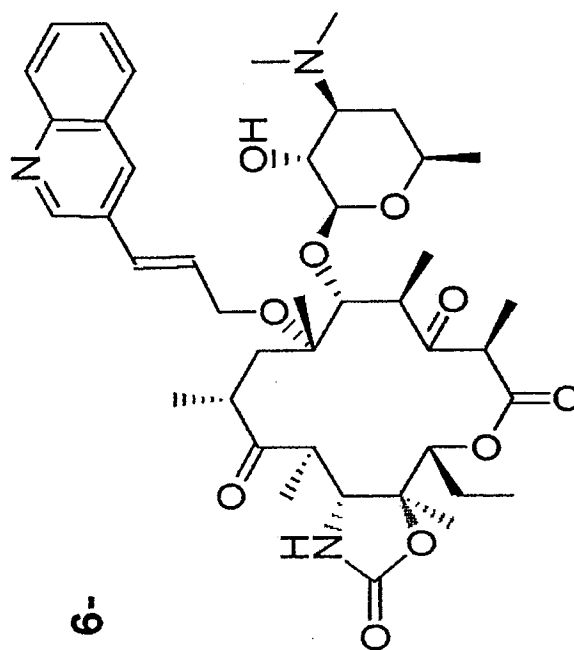




**ABT-773**

**The Molecule**

# ABT-773 Ketolide



•Quinolylallyl propenyl moiety at the 6-  
0 -position

•Keto group at the 3-position

•Carbamate group at the  
11, 12-position

ABT-773

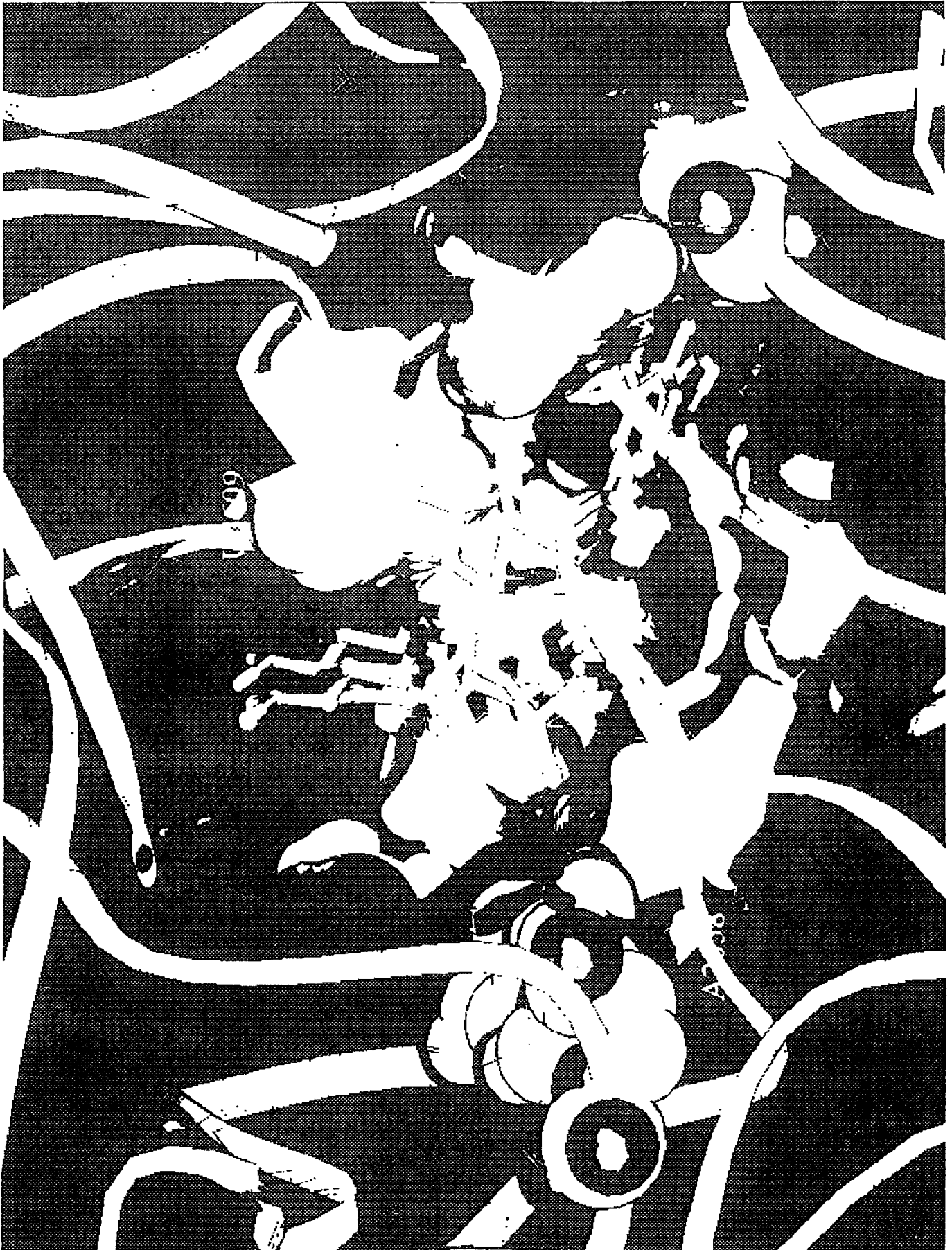


## ABT-773 Ketolide

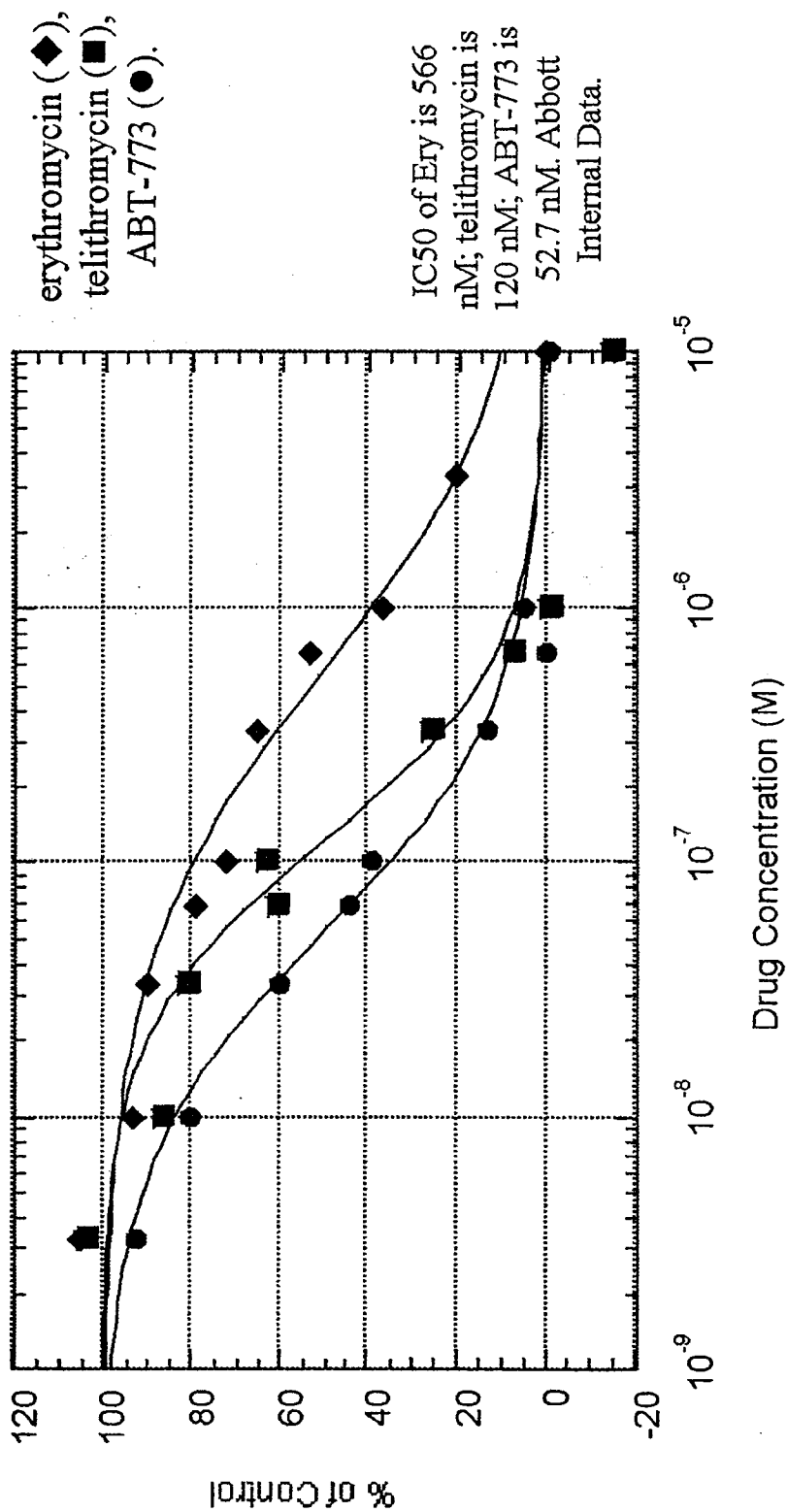
- **Ketolides are a Novel Class of Antimicrobial**
  - Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development

# Microbiology

Organism	MIC <sub>90</sub> $\lambda$ g/ml			
	ABT-773	Ketek	Clari	Azi
<i>S. pneumoniae</i> ery-S	0.008	0.004	0.03	0.12
<i>S. pneumoniae</i> mef	0.12	1.0	4.0	16.0
<i>S. pneumoniae</i> erm	0.01	0.12	>32	>32
<i>S. pyogenes</i> ery-S	0.12	2.0	1.0	2.0
<i>S. pyogenes</i> ery-R	0.5	>8.0	>32	>32
<i>M. catarrhalis</i>	0.25	0.25	0.5	0.25
<i>H. Influenzae</i>	2.0	2.0	16	2.0
Legionella	2.0	2.0	0.06	1.0
<i>M. Pneumoniae</i>	<0.005	<0.005	0.008	<0.005
<i>C. Pneumoniae</i>	<b>0.015</b>	0.06	0.06	0.12

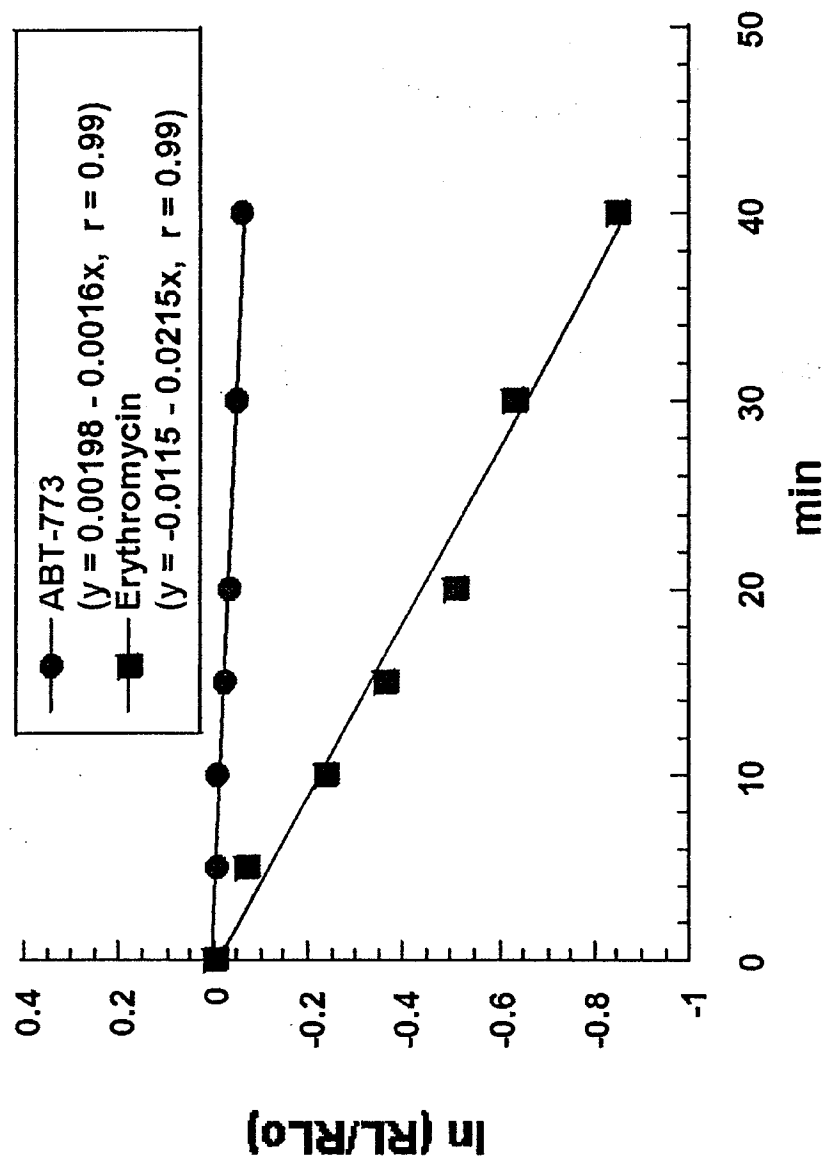


# Ribosome Binding, Susceptible *S. pneumoniae*

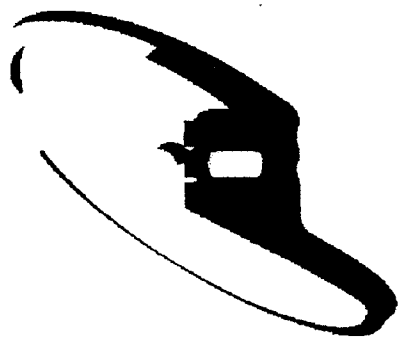




# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.



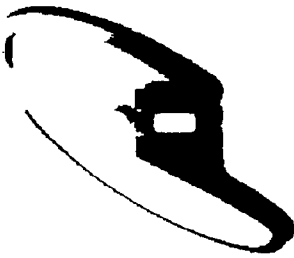
# QTc potential and Liver Toxicity Issues



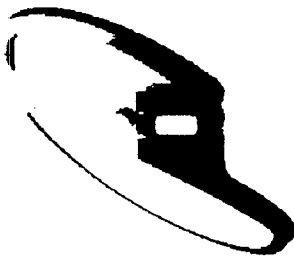
## QTc Prolongation Issues

- Potential for QTc Prolongation is a hot button worldwide
  - Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies
  - ICH guidelines require data from animal models and 200 patients
  - FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
  - FDA has question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QTc
  - Required to include ECG monitoring in pivotal Phase 3 studies
  - FDA may require a Phase I study in patients with underlying cardiac disease
  - Some antimicrobials now contain warnings for QT prolongation
  - Telithromycin (Ketek) data residing at FDA
    - Advisory Meeting rescheduled to May 2001 probably not related to QTc concerns

## QT<sub>c</sub> Prolongation Issues ABT-773



- Pre-clinical data positive for QT<sub>c</sub> dose response.
- A possible dose effect in Phase I at total daily dose  $\geq 800$  mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 C<sub>max</sub> 5X)
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)



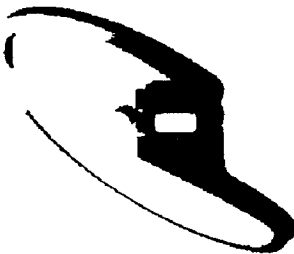
## **QT<sub>c</sub> Prolongation Issues ABT-773 Plan**

- Completed pre-clinical evaluation of ABT-773
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Planning FDA requested study of QTc in patients with pre-existing cardiac disease.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.



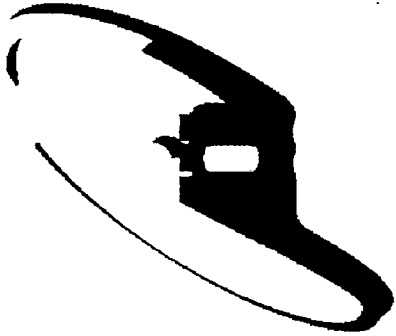
## Liver Toxicity Issues

- Potential for liver toxicity is a concern for the FDA
  - Recent liver toxicity seen with Trovofloxacin are of concern to regulatory agencies.
  - Gemifloxacin recently not approved by FDA because of liver toxicity concerns.
  - FDA meeting on guides to industry on how to study liver function scheduled for February 11-12, 2001



## **Liver Toxicity Issues for ABT-773**

- Preclinical tox showed some effect on the liver function.
- Japanese in bridging study showed increased LFTs.
- No evidence of LFT issue in Western subjects.
- No evidence of dose response.
- Repeat of Japanese bridging study in Japan showed No evidence of LFT increases in Japanese or Caucasians.
- ABT-773 plan for accessing problem
  - Continue to monitor LFT in Phase III programs.
  - Jean Fox will attend FDA meeting.



# Phase III Program

# Phase III Program

## Proposed Indications and Treatment Duration

Infection	Dosage	Duration
Pharyngitis/Tonsillitis due to: <i>S. pyogenes</i> *	150 mg QD	5 d
Acute bacterial sinusitis due to: <i>H. influenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i> **	150 mg QD or BID 150 mg QD or BID 150 mg QD or BID	10 d 10 d 10 d
Acute bacterial exacerbation of chronic bronchitis due to: <i>H. influenzae</i> <i>H. parainfluenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i> **	150 mg 150 mg 150 mg 150 mg	5 d 5 d 5 d 5 d
Community-acquired pneumonia due to: <i>C. pneumoniae</i> <i>H. influenzae</i> <i>L. pneumophila</i> <i>M. pneumoniae</i> <i>S. pneumoniae</i> **	150 mg QD or BID 150 mg QD or BID 150 mg QD or BID 150 mg QD or BID 150 mg QD or BID	10 d 10 d 10 d 10 d 10 d

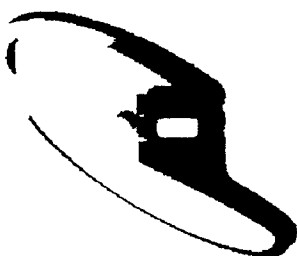
\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.

## Phase III Program *Studies Started in Year 2000*

Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	185/520	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	0/520	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	131/600	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	0/500	EU (Non-IND)





## Phase III Program Studies Started in Year 2000, Con't

### Dose Finding Studies for Sinusitis/CAP:

Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	137/500	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	76/500	US, Canada, EU (IND)

# SDG Analysis of Ph. III CAP Development Options

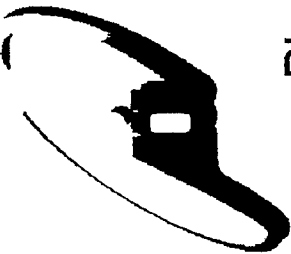
CAP Development Strategy	Timeline Impact	Incremental Cost	Relative Regulatory Risk	Potential for 150 mg. QD in CAP
1. 150 mg QD only Ph. III (Begin now)	8/2002	0	High	Yes
2. Further Phase II 150x dose ranging, then Phase III	8/2002	\$5.4M	Low	Yes
3. Parallel Phase III program for 150 mg QD/150 mg BID	8/2002	\$7.43M	Low	Yes
4. 150 mg BID only Ph. III (Begin now)	8/2002	0	Mod	No
5. 300 mg QD only Ph. III (Begin now)	8/2002	0	Low	No
6. Phase III open-label dose ranging	8/2002	\$7.2M	Low	Yes

Selected Strategy

Positive Factor

Neutral Factor

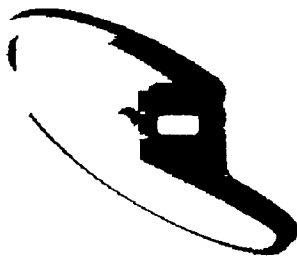
Negative Factor



## **Dosing Issue**

### **150 mg BID vs 150 mg QD: Background**

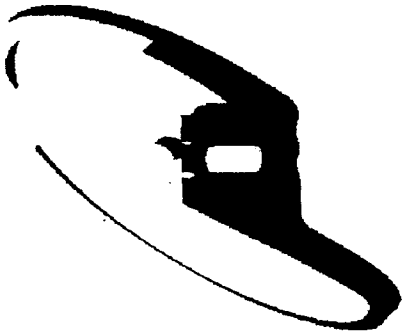
- Phase II data indicated 300 mg QD was not viable due to high levels of diarrhea (10-20%) and taste perversion (10-20%)
- Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD
  - 150 mg QD currently being evaluated in ongoing phase III trials in these indications
- Dosing selection for CAP and sinusitis confounded by limited data
  - few bacterial isolates, particularly with H. flu, in sinusitis
  - no 150 mg arm in CAP trial
- To increase probability of correct dose selection in CAP/sinusitis, additional studies are ongoing to generate more data in these indications
  - 150 mg QD vs 150 mg BID CAP & sinusitis trials ongoing



# Dosing Issue

## 150 mg BID vs 150 mg QD: Implications of Decision

- Regulatory and commercial environments differ dramatically between U.S. and ex-U.S.
  - For U.S., market:
    - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
    - Approval on indication-by-indication basis
    - Optimal strategy for U.S. may be to pursue QD dosing for CAP/sinusitis
  - For ex-U.S. market:
    - CAP data represents the “lynchpin” for approvability of the entire molecule, hence a conservative BID approach may result in lower regulatory/commercial risk
    - Relatively minor commercial impact of BID dosing
    - Optimal strategy for ex-U.S. may be to pursue BID dosing for CAP and perhaps sinusitis
- A decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01
  - Data may not show a clear “winner” due to relatively low power of studies; may be a difficult decision
  - Due to soft global flu season and protocol amendments, enrollment is behind plan and could impact timing of decision
- A plan to have divergent US/Ex-US clinical programs in CAP/sinusitis may be required to minimize regulatory / commercial risks
  - Cost / timeline implications



# ABT-773 IV Program

Once-daily  
**Zithromax® I.V.**  
 (azithromycin for injection)

The only I.V. advanced-generation  
 macrolide for community-acquired  
 pneumonia\* in adult hospitalized patients

Targeted coverage of the key pathogens of  
 community-acquired pneumonia

Typical	Atypical
<i>Streptococcus pneumoniae</i>	<i>Legionella pneumophila</i>
<i>Haemophilus influenzae</i>	<i>Chlamydia pneumoniae</i>
<i>Staphylococcus aureus</i>	<i>Mycoplasma pneumoniae</i>
<i>Moraxella catarrhalis</i>	

Proven as effective as  
 cefuroxime ± erythromycin

Early step-down therapy to oral Zithromax

Very well tolerated

The most common side effects associated with treatment  
 in adult patients who received I.V. Zithromax in studies  
 of community-acquired pneumonia were gastrointestinal  
 effects (nausea, 3.6%; abdominal pain, 2.7%), and  
 vomiting (1.1%). The most common side effects related to  
 Zithromax included pain at the injection site (6.3%) and mild  
 inflammation (3.1%).

Zithromax is contraindicated in patients with known  
 hypersensitivity to azithromycin, erythromycin, or any  
 macrolide antibiotic.

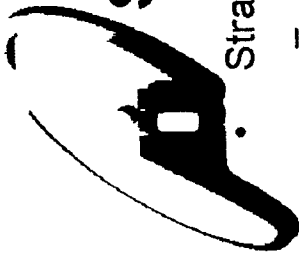
Once-daily  
**Zithromax® I.V.**  
 (azithromycin for injection)  
 by Zeebra

The Power of Z in I.V.

The Power of  
**Z**  
 in I.V.

\*Zithromax I.V. is indicated for community-acquired pneumonia  
 due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella*  
*pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*,  
*Staphylococcus aureus*, or *Streptococcus pneumoniae* in patients  
 who require intravenous therapy.  
 In a controlled study of 281 hospitalized patients with community-  
 acquired pneumonia, Zithromax (500 mg i.v. single daily dose for the  
 first 3 days, followed by 250 mg i.v. single daily dose for the next  
 5 days, followed by 500 mg i.v. single daily dose for the next 5 days)  
 was compared with cefuroxime (750 mg i.v. single daily dose for the first 3 days,  
 followed by 500 mg i.v. single daily dose for the next 5 days) and  
 erythromycin (250 mg i.v. single daily dose for the first 3 days,  
 followed by 500 mg i.v. single daily dose for the next 5 days).  
 Zithromax was superior to both cefuroxime and erythromycin in  
 terms of clinical response and tolerability.

Please see brief summary of prescribing information  
 on last page of this advertisement.



# ABT-773 IV Formulation Strategic, Commercial, and Technical Value

## Strategic Value

- IV represents a channel not currently served by Anti-infective Franchise
- Leverages presence of Medical Center Reps and experience with ID community

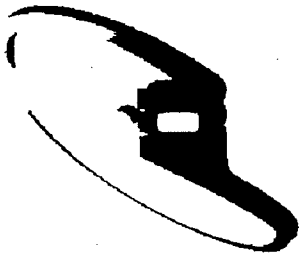
## Commercial Value

- IV availability figures favorably into decisions regarding formulary access to molecule
  - potential advantage over telithromycin, which will not have an IV
  - required to compete effectively with Zithromax, Tequin, Avelex which have IVs
- Positive impact on tablet formulation
  - estimated \$36MM incremental to peak tablet sales due to step-down therapy
  - Enhances overall “potency” image of brand

## Technical Value

- Support for *S. pneumoniae* Resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provides additional information on QT effects

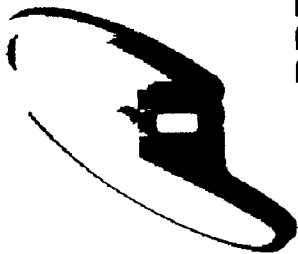
IV launch currently lags tablet launch by 1 year; any further delays will reduce the potential value



## **ABT-773 IV Program Formulation Objectives**

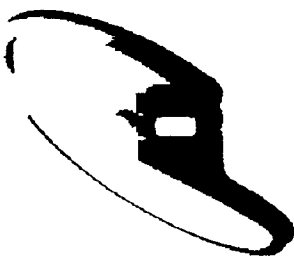
- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counter ion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.





## **ABT-773 IV Formulation PPD/HPD Funding Status**

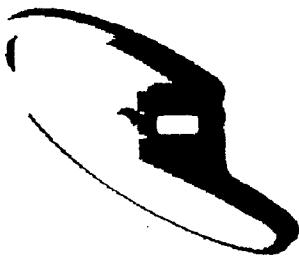
- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV (\$7MM)
  - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)



## **ABT-773 IV Formulation**

### ***Animal Pain Study Results***

- Assessed 6 prototypes (3 different counter ions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
  - Results not conclusive
  - Need to evaluate in humans
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.



## **ABT-773 IV Planned Clinical Program**

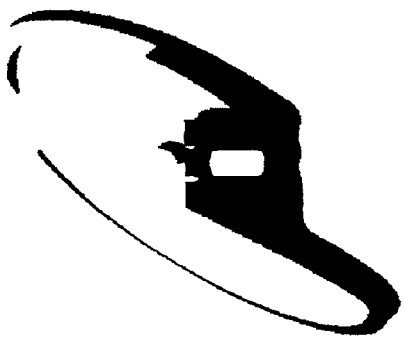
*With 2001 funding decision in Feb:*

- |  |         |
|--|---------|
| • Single Dose-rising Phase I study         | Apr/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND                              | Oct/01  |
| • Initiate Phase III                       | Dec/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |

## ABT 773 IV Program Summary

- **Comments**

- Funding for '01 not available PPD/HPD
- Go/No go could be made after Phase I based on safety profile (pain, QT, GI)
- Milestone funding recommended (\$1MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant *S. pneumo* claim
- Total Program Cost 2000-2003 (\$22.5MM)



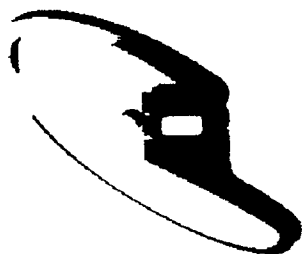
# Pediatric Program



## **ABT-773 Pediatric Formulation**

### **Importance to the 773 program**

- Increased perception of safety
- Better pricing and acceptance in European markets
- FDA requires studies in pediatrics



## **ABT-773 Pediatric Program Formulation Objectives**

- Develop coated particle formulae for global use
  - coated particles for Suspension - 150mg/5mL & 300mg/5mL
  - coated particles as a dry syrup, sprinkle or sachet.
- Desired Properties
  - Once a Day Dosing
  - Acceptable 'Initial Taste'
  - Minimal 'After Taste'
  - No Unpleasant Mouth-feel
  - Acceptable Color and Flavor
  - No Refrigeration Required.

# ABT 773 Pediatric Program

## Taste Assessment

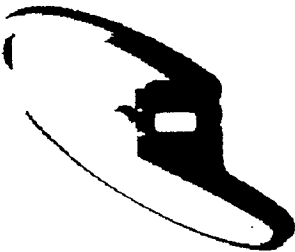
### Sensory Analysis of Uncoated Drugs *Summary of Results*

The three drug substances can be ranked from most to least bitter as follows:

Drug Substance	Concentration (ppm) which Exhibits an Initial Bitter Intensity <4 (Slight)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

- ABT-773 is approximately five times more bitter than clarithromycin

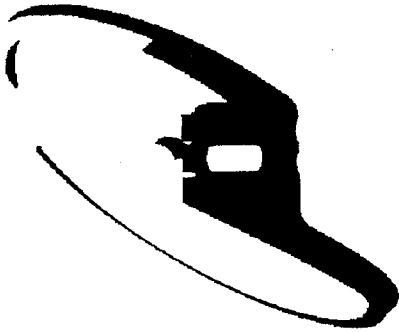




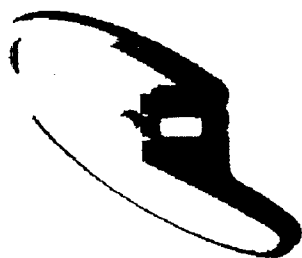
## **ABT 773 Pediatric Program**

### ***Taste Assessment***

- The ABT-773 encapsulated prototype #2 may be at risk of dosing compliance problems due to flavor quality.
- Overall ABT-773 Prototype 2
  - Less bitter than Biaxin both initial and after taste
  - More bitter than Zithromax both initial and after taste
- For ABT-773 Prototype 2, the flavoring aromatics and sweetness decay quickly, exposing the bitterness which lingers throughout the aftertaste at or above the “concern” intensity level.

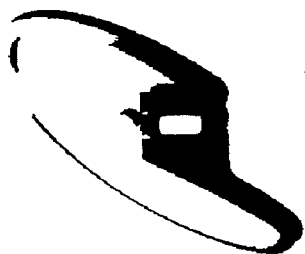


# Japan Program



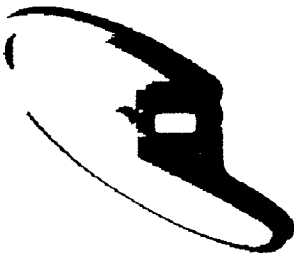
## Japan Program Taisho

- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan



## Japan Program Clinical Plan

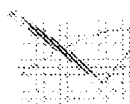
<ul style="list-style-type: none"><li>• Phase I in Japan<ul style="list-style-type: none"><li>– Food Effect Study</li><li>– Single and multiple dose study</li><li>– Review data (Abbott/Taisho)<ul style="list-style-type: none"><li>• PK data Japanese vs Caucasian</li><li>• Development program strategy</li></ul></li><li>– Present Kiko data and recommend development program May/01</li><li>– Start Tissue Conc. Study</li></ul></li></ul>	<u>Start</u> Completed  Completed  April/01    2Q/01
--	---



## **Japan Program Clinical Plan**

- PK similar in Japanese and Caucasians (12/02 filing)
  - Recommend to Kiko same dose in Japan as in ex-Japan
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in skin infections, dentistry, otolaryngology, UTI and pan-bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians (12/03 filing)
  - Phase II dose ranging study in CAP (Bridging study)
  - Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing





Eugene X  
Sun/LAKE/PPRD/ABBOTT  
02/22/2001 06:57 PM

To Stan Bukolzer/LAKE/Al/ABBOTT@ABBOTT  
cc  
bcc  
Subject 773 material

Stan,  
here are some background materials



ABT-773 Development Plan 1.doc



Leiden review Dec00.ppt



End of Phase 2 Meeting Minutes.doc



End of Phase 2 Meeting - Primary Slides.ppt



ABT773 Review Pharma Exe Meeting.rtf



ABT-773 Pharma Exe Meeting.ppt

# **ABT-773 DEVELOPMENT PLAN**

C. Meyer [DATE]



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## A. Executive Summary

### A.1 SWOT Analysis

Table A.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<p>ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Erm AM and Mef phenotypes; it has not been shown to induce MLS<sub>B</sub> (macrolides, lincosamides and streptogramin B) resistance.</p> <p>The in vitro microbiological profile of ABT-773 shows a 4-fold superiority to telithromycin which should translate into 3 to 5 times lower daily dose than the first ketolide.</p>	<p>Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.</p> <p>Capitalize on micro superiority and lower dose by generating comparative efficacy/safety data in Phase IIIb studies.</p>
Weaknesses	<p>Pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged.</p> <p>In Phase IIb studies, 300 mg QD has higher GI/taste perversion adverse events compared to clari 500 mg BID</p> <p>The Phase III clinical program is large, intense, and must be conducted successfully in a relatively short period of time. There is also very stiff competition from other major pharmaceutical companies to enroll patients. Many of these companies are paying inflated grants fees and have simpler Phase IV protocols that will entice investigators.</p> <p>An IV and pediatric formulation will not be available at launch. An IV formulation would further enable us to position this product as an effective drug for a range of mild to severe infections. A pediatric formulation would further underscore the safety properties of the product. Both formulations would promote improved acceptance of this product.</p>	<p>Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure.</p> <p>Monitor enrollment closely and be proactive with CROs in opening additional sites and offering appropriate incentives to push enrollment. Prepare to open sites in the Southern hemisphere.</p> <p>HPD has identified initial funding this year to bring an IV prototype into Phase I studies. Further development funding has been requested in 2001 in the IIPD plan and has been included in a PTD blue plan request.</p> <p>Present initial pediatric Phase I data as well as taste evaluation will be available mid-October for management decision on future funding.</p>
Opportunities	<p>ABT-773 has the potential to be able to address competition with azithromycin with short course therapy for mild infections, as well as quinolones for more serious infections. Resistance (PRSP/MRSP) is a growing concern and will be a major consideration when this product is introduced.</p>	<p>Conduct appropriate comparative Phase III studies to get approval for all the RTI indications, both in U.S. and European countries. Collect enough resistant isolates to obtain the claim for resistant <i>S. pneumoniae</i>.</p>

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	<p>If 150mg QD is proven effective, COGs for this product will be within a very acceptable range for obtaining a high profit margin in all markets.</p> <p>Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i>.</p>	<p>Continue to improve throughput and yield and introduce appropriate process improvements in SPD to further bring down the bulk drug costs. Propose intermediate step 5 as the starting material for the bulk drug to enable further process improvements post-filing.</p> <p>This opportunity exists for the FDA labeling only and recent information indicates that FDA is rethinking their position on granting this separate claim. Other antibiotics have been granted this claim with as little as 15 isolates.</p>
<b>Threats</b>	<p>Current data available is insufficient to predict that 150mg QD will be effective in more serious indications of CAP and Sinusitis. Current two dose studies are being carried out in 150mg QD and 150mg BID to assess the potential of 150mg BID being the required dose for these indications.</p> <p>Regulatory uncertainties over how to deal with ketolide/macrolide class</p> <p>Elevated liver enzymes were seen in a small number of Japanese volunteers in a PK study.</p> <p>The Japanese development program has been delayed due to findings in the first Japanese PK study indicating a significant difference in the PK profiles between Japanese and non-Japanese subjects. Timing, dose selection and funding for the Japanese program is unknown at this time.</p>	<p>May need to market 150mg QD for mild infections and 150mg BID for more severe infections.</p> <p>ABT-773 is similar to clarithromycin and erythromycin in its effect on QT intervals in preclinical studies. Current clinical data indicates no evidence of QTc prolongation. ECG monitoring is included in all the Phase III studies. An IIPD funded phase I study of an IV formulation prototype will provide additional information on QTc prolongation.</p> <p>Current expert analysis has concluded that there no clinically significant interaction. The study is being repeated in Japan to further evaluate.</p> <p>Repeat Japanese PK study in Japan along with a food effect study. Once results are available, meet with clinical advisory committee KIKO and determine the development requirements for Japan.</p>

## A.2 Development Plan Summary

Considering the rapid and extensive emergence of penicillin and macrolide resistant *S. pneumoniae*, and the remaining patent life of Clarithromycin, the flagship of Abbott's pharmaceutical product line, ABT-773 was approved by PPCC in 03/97 as a candidate for Development by the Anti-Infective Venture. The mission of the Venture is to develop ABT-773

7

as a first line therapy in community acquired lower and upper respiratory infections (RTIs).

The proposed indications and treatment durations below position this product to compete effectively in the RTI arena both in the U.S. and in international markets. These are the required indications to be considered as first line therapy for RTIs.

- |  |         |
|--|---------|
| • Community-Acquired Pneumonia                       | 10 Days |
| • Acute Bacterial Sinusitis                          | 10 Days |
| • Acute Bacterial Exacerbation of Chronic Bronchitis | 5 Days  |
| • Acute Streptococcal Pharyngitis/Tonsillitis        | 5 Days  |

Our goal is to provide the physician with an agent which will have the safety and tolerability of azithromycin for mild to moderate infections but with the strengths of the quinolones for moderate to severe infection of the respiratory tract particularly for (PRSP/MSRP) resistant *S. pneumoniae*.

We will also be seeking additional labeling to include the treatment of macrolide-resistant *Streptococcus pneumoniae*, penicillin-resistant *Streptococcus pneumoniae*, and atypical pathogens to include *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* in the above-mentioned indications. Susceptibility and clinical treatment trial data for macrolide-resistant *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae* will be provided from Phase 3 trials. A request for appropriate breakpoints to include these strains will also be provided in the NDA.

**B. Marketplace****B.1 Marketplace SWOT Analysis**

<b>Table B.1a SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)</b>		
<b>CATEGORY</b>	<b>ITEM (Probability/Impact)</b>	<b>STRATEGY</b>
<b>Strengths</b>	Large market in terms of both prescriptions and sales	None
	Emerging international markets may contribute to positive market growth ex-U.S. Antibiotic resistance ultimately renders older agents obsolete, allowing newer agents access to the market	Move forward with global development program Target resistance claim for ABT-773
<b>Weaknesses</b>	May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance	Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS)
	Difficult to differentiate antibiotics High hurdle rate for new agents in terms of convenience and adverse event profile High level of promotional support required to reach optimal sales levels	Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy Evaluate ABT-773 profile upon receipt of phase III data Build adequate promo levels into LRP
<b>Opportunities</b>	ABT-773 represents a hedge against Biaxin IR patent expiration in 2005	Evaluate optimal portfolio/promo strategy between Biaxin XL and 773 in light of patent expiration
	Potential for I.V. formulation, expands scope of franchise into new market segment Potential for pediatric formulation	Continued funding of IV program Make go/no-go decision based on taste/PK data
<b>Threats</b>	Telithromycin launch 2-1/2 years in advance of ABT-773	Monitor launch of telithromycin, adjust 773 strategy if necessary based on market feedback
	Considerable number of antibiotics lose patent exclusivity by 2005-may put negative price pressure on market May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance New entrants	Work with managed care group to evaluate potential impact Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS) Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy

## B.2 Epidemiology/Disease Class

Respiratory tract infections represent the majority of community-acquired infections. Causative pathogens for these infections are most often *Strep. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *M. pneumoniae*. Table X summarizes the annual incidence of community-acquired respiratory infections.

Table B.2.1: Annual Incidence of Community-Acquired Infections

	Infection	Annual Incidence (U.S., millions)	Annual Incidence (Ex-U.S., millions)
Upper Respiratory	Sinusitis	37	94
	Otitis	18	46
	Pharyngitis	12	30
Lower Respiratory	Bronchitis	14	36
	Pneumonia	4	10

## B.3 Market Overview

### U.S. Market

1999 U.S. antibiotic prescription and sales data are presented in the table below.

			1995	1996	1997	1998	1999	CAGR <sub>95-99</sub>
U.S.	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

The macrolide class has grown significantly over recent years, from \$771MM in 1995 to \$1,596MM in 1999, though most of this growth (\$673MM) was due to gains in Zithromax, underscoring the importance of convenience, adverse event profile, and price in this market.



**Ex-US Market**

The ex-US antibiotic market had sales of \$11.6B in 1999, an increase of approximately 5.9% over 1998; however the CAGR over the past 3 years has been only 0.7%. Antibiotic usage is expected to decline 1-2% per year in the largest, most developed AI regions – Europe, Japan and Canada; however, Latin America and PAA are expected to show 1.5% - 3.0% growth as access to healthcare continues to improve. Standard units (used as a proxy to normalize units across regions) have decreased approximately 1.7% versus prior year, despite strong sales growth. This reflects a gradual shift to newer, premium priced agents, particularly in less developed regions.

Clarithromycin performance in AI markets continues to be strong, out-performing azithromycin sales and growth rate by almost 3 to 1. Although the ex-US quinolone class market share (15.3%) significantly lags US performance (28.4%), the quinolones show strong growth, fueled in part by new product introductions such as levofloxacin. It should be noted, however that almost 80% of Levo sales are in Japan, where sales increased 40% over the previous year. Levo launched in 1994 in Japan, but has only recently been introduced in other ex-US markets. Moxifloxacin was launched Q4 1999 in Germany, and has begun roll-out to other European markets in 2000. Moxi has not yet been submitted in Japan. Gatifloxacin approval is expected for European markets in Q2 2001, and is currently in Ph III for Japan. Cephalosporins continue to dominate the ex-US market, with sales share of over 40% (compared to only 17% in the US).

**Table B 3.b Ex-US Sales**

	1999 Sales			1999 Standard units		
	Sales (\$000s)	Share	Growth (99/98)	SU (000s)	Share	Growth (99/98)
<b>Penicillins</b>	<b>\$2,475</b>	<b>21.2%</b>	<b>0.8%</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>
Augmentin	\$684	5.9%	1.9%	1,213	6.4%	2.0%
Amoxicillin	\$684	5.9%	-8.1%	3,479	18.3%	-1.9%
<b>Cephalosporins</b>	<b>\$4,948</b>	<b>42.3%</b>	<b>7.5%</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>
Cefaclor (Ceclor)	\$344	2.9%	-8.0%	638	3.4%	-8.9%
Cef. Axetil (Cefin)	\$288	2.5%	2.9%	261	1.4%	2.7%
Cef. Proxetil (Vantin)	\$185	1.6%	7.0%	186	1.0%	3.9%
<b>Ext. Spec. Macrolides</b>	<b>\$2,257</b>	<b>19.3%</b>	<b>5.1%</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>
Clarithromycin	\$904	7.7%	12.0%	816	4.3%	8.3%
Azithromycin	\$344	2.9%	4.1%	113	0.6%	4.6%
Roxithromycin	\$253	2.2%	0.1%	257	1.4%	-0.8%
<b>Quinolones</b>	<b>\$1,788</b>	<b>15.3%</b>	<b>11.1%</b>	<b>NA</b>	<b>NA</b>	<b>NA</b>
Ciprofloxacin	\$530	4.5%	1.2%	404	2.1%	4.7%
Levofloxacin	\$467	4.0%	54.0%	248	1.3%	31.2%
<b>TOTAL</b>	<b>\$11,685</b>	<b>100%</b>	<b>5.9%</b>	<b>19,031</b>	<b>100%</b>	<b>-1.7%</b>

Source: IMS retail pharmacy data for all formulations, all audited ex-US markets; standard units used as a proxy for prescription market share, since Rx's are not audited in most ex-US markets

**B.4 Current Treatment Options**

Class	Mechanism of Action	Comments
Penicillins	Cell wall synthesis inhibitor	Mostly generic, class has seen significant decrease as a result of penicillin resistance
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications
Sulfonamides	Folic acid synthesis	Generic agents, relatively high levels of resistance but are still useful in some indications
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; H. flu activity continues to be class weakness, along with GI events, drug-drug interactions, & taste perversion
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram+ profile and potential safety issues will be used primarily in nosocomial setting

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**B.5 Competitive Analysis – Emerging Competition**

<i>Table B.5a Pipeline</i>					
<i>Product</i>	<i>Company</i>	<i>Class</i>	<i>Phase/Estimated Time to Market</i>	<i>Country</i>	<i>Comment</i>
Ketek (telithromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3000; 800 mg QD; first in ketolide class to reach market
Factive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est. launch 12/00	US	Superior to other quinolones for MRSA; highly potent vs. RTI pathogens H. flu, M. cat, and S. pneumo and UTI pathogens E. coli and P. mirabilis, CRSP; potency > spar, trov, grep and ≥ trov; activity vs. P. aeruginosa; good atypical and mycoplasma coverage; intracellular penetration; low photo/CNS tox; /00 patient database
Sitafloxacin	Daiichi Sankyo	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Potent against MRSA, pseudomonas and bacteroides activity; diarrhea, A/T, low WBC; phototox issues; will likely target severe rather than community infections
Econofloxacin	Chiesi Foods	Quinolone	II Est. launch 2002	UK	Active against UTI and RTI pathogens; superior to lome and oflo vs. P. aeruginosa. T <sub>1/2</sub> = 14-19 hrs will likely be target to severe rather than community infections
CS-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G+/G-; excellent activity against H. flu, n. jejuni, M. pneumoniae, and C. trachomatis; greater potency than ciproflox > 7 hr; BA=80%
T-3811	Toyama/BMS	Quinolone	I Est. launch 2005	Japan	Excellent potency and low toxicity
ABT-192	Abbott	Quinolone	Pre-clin Est. launch 2005	US	Excellent potency, good anti-pseudomonal activity. To initiate phase I (11/00)
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est. launch 2006	Japan	Low toxicity; in vitro potency ≥ trov, STX & HSR-903

**B.6 Unmet Needs**

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation. Table B.6a shows the impact of the pipeline on current unmet market needs.

<i>Table B.6a Unmet Market Needs and the Impact of the Pipeline</i>	
<i>Unmet Need</i>	<i>Pipeline Impact</i>
Activity against resistant organisms	Strep. pneumo, MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant Strep. pneumo strains; quinolone-resistant Strep. pneumo may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gariloxacin claims 8-methoxy functional group results in lower propensity for resistance development
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety profile should be regarded as a necessary component rather than a differentiating one
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market

## C. Product Positioning

### C.1 Product Positioning Options

Positioning Alternative	Strategy	Strengths	Weaknesses
Macrolide replacement	Convert existing macrolide business (including Biaxin) to ABBT-773. Desirable if Biaxin XL erosion is expected to be high upon launch of IR generics	Relatively simple strategy to implement & communicate to market  Large Zillarennix business to target  Strategy is a natural extension of 773's activity against macrolide-resistant <i>S. pneumoniae</i>	Sales are at expense of Biaxin  Will need to achieve a very good tolerability & convenience profile to maximize this strategy  May be difficult to keep business from shifting toward generic clarithromycin
Second Line (macrolide sparing)	Coposition Biaxin and ABBT-773. Desirable if Biaxin XL erosion is expected to be low upon launch of IR generics	Sales of 773 would be at least partially additive to Biaxin  Support of both Biaxin and 773 may allow a broader scope of the RTI market to be served  Allows for greater flexibility with price, potential for advantageous price/volume scenarios	Can be difficult to segment & communicate to reps/physicians
Quinolone fighter	Position as a potent alternative to quinolones for RTIs	RTI-specific spectrum of 773 could play well if quinolone resistance develops  RTI-specific spectrum of 773 is consistent with "appropriate use"  Quinolones are fast-growing market segment	May be difficult to convince physicians that 773 is as potent  H. flu activity of 773 is inferior to quinolones

## C.2 Target Product Profile

### C.2.1 ABT-773 Target Product Profile

Table C.2.1 outlines the desired target product profile for ABT-773

Product Profile					
Attribute	Date Defined	Probability*	Confirm Status	Share Impact	
Activity against Gram + Gram - atypicals	3/1997	High	Confirmed	High	
Activity against <i>H. influenzae</i> = azi	3/1997	High	Confirmed	High	
Active against 80% of Gram + resistant strains of efflux and MLS-c	3/1997	High	Confirmed	High	
Active against most macrolide resistant pathogens on a bacterial-workforce-susceptibility panel	3/1997	High	Confirmed	High	
Incidence of GI side effects=azi	3/1997	Low	Not Met	High	
Incidence of drug interactions = clar, no contraindications	3/1997	High	6/2001	Medium	
QD dosing adult/child	3/1997	Medium	6/2001	High	
QD dosing oral CS	2/1997	Medium	9/2000	Medium	
QD dosing for IV	3/1997	Medium	12/2000	High	
Comparable pain at injection site than azi		Medium	12/2000	Low	
Less metallic taste than clar XL	3/1997	Medium	6/2001	High	
CS equivalent taste to Azi Omnicel		Low	9/2000	High	
5 day therapy for most indications	3/1997	Low	6/2000	High	
COGS > 80% SMM at launch	3/1997	High	12/2001	Low	
Maintain balanced plasma/tissue levels similar to clar		Medium	12/2001	Medium	

\* Probability Key:  
 High = 70-100%  
 Medium = 30-69%  
 Low = 0-29%

Table C.2.2 outlines the product profile strengths, weaknesses, opportunities and threats.

<b>Table C.2.2 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)</b>		
<b>CATEGORY</b>	<b>ITEM (Probability/Impact)</b>	<b>STRATEGY</b>
<b>Strengths</b>	Macrolides/ketolides are regarded as an "appropriate" choice for RTIs; could be used to advantage should quinolone resistance develop	Leverage recent guidelines to develop support for class in RTIs; monitor quinolone resistance surveillance
	ABT-773 is generally regarded as more potent than telithromycin and macrolides against Gram positive causative RTI pathogens, including resistant pathogens	Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin and other agents via advisory panels, symposia, etc.
	ABT-773 may offer unique mechanistic advantages relative to telithromycin and macrolides (ribosome binding)	Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin via advisory panels, symposia, etc.
<b>Weaknesses</b>	Potential for perceived weakness of product with respect to PK profile at 150 mg dose	Identify strategy to "explain" clinical data in light of PK issue; "ribosome story"
	H. flu microbiological activity inferior to quinolones	May be able to mitigate if clinical eradication data is strong; re-evaluate after receipt of phase III data
	Phase II data suggests moderate levels of diarrhea and taste perversion	Telithromycin appears to have even higher diarrhea rate; consider phase IIIb/IV comparative study
<b>Opportunities</b>	Potential for I.V. formulation, has positive impact on image of tablet	Continued funding of IV program
	Potential for pediatric formulation, has positive impact on image of tablet	Make go/no-go decision based on taste/PK data
<b>Threats</b>	May be BID dosing for CAP and/or sinusitis-all recent antibiotics have QD dosing for all indications	Proceed with dose ranging phase III to determine if QD dosing is adequate for these indications
	H. flu eradication may be sub-standard at 150 mg dose	Evaluate in light of phase IIIa data (2Q01)
	Telithromycin may gain 5-day indication for sinusitis-no other antibiotics have 5-day claim	In light of phase IIIa data, evaluate whether 5-d vs 10-d ABT-773 arm could be added to gain 5-day indication
	Requisite number of resistant isolates for claim may not be achievable for NDA; may require additional trials	Evaluate situation at completion of phase III clinical program

**C.2.2 Target Product Label - See Appendix 1**

**C.3 Reimbursement/Pricing Strategies**

**C.3.1 Reimbursement/Managed Care**

Development of reimbursement strategies will be initiated upon completion of the phase IIIa studies, at which time product dosing will have been determined and more certainty to efficacy/AE rates will have been obtained.

**C.3.2 Pricing Strategy**

- a) U.S pricing for 5 days of ABT-773 will be at parity with 5 days of Zithromax, allowing ABT-773 to effectively compete for Zithromax business.
- b) Pricing in most European markets will be set by the government, and will be somewhat dependent on how the ketolide is classified – as a macrolide or as a new class that merits a price premium vs. the macrolide class. Although a price premium would increase revenue per unit, it could potentially limit market penetration, and therefore, reduce total revenue opportunity. Clari will be subject to downward pricing pressure due to European and Japanese price control measures and to generic incursion in LA and PAA markets over the next few years. Therefore, the base case pricing assumption is that ABT-773 will achieve pricing comparable to current clari price per course of therapy.



**C.4 Sales Forecast(s) for ABT-773****C.4.1 U.S. Sales Forecast**

The U.S. forecast is shown in Table C.4.1a, below:

<b>Table C.4.1a U.S. Forecast (Date of Forecast: 7/00)</b>					
	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>
Market (MM TRX)*	195	193	191	189	187
- % chg	-1.0%	-1.0%	-1.0%	-1.0%	-1.0%
Abbott Share (%)	2.1%	3.2%	4.2%	5.3%	6.2%
Abbott TRX (MM)	4.1	6.2	8.1	10.0	11.7
Price/Rx (\$ avg)	\$35	\$34	\$32	\$33	\$34
Abbott Sales (\$MM)	\$139	\$199	\$265	\$335	\$399
R&D (\$MM)	\$30	\$30	\$30	\$30	\$20
SG&A (\$MM)	\$101	\$83	\$86	\$99	\$115
SMM (%)	88%	90%	90%	90%	91%
Div. Margin (\$MM)	(\$23)	\$44	\$95	\$138	\$174

10 year pre-tax NPV @ 12.5% = \$345MM

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$201MM

10 year post-tax ENVY @ 12.5% = TBD

**Key Assumptions:**

- U.S. approval August 2003
- Market is declining 1% per year on TRX basis
- 150 mg QD dosing for all indications
- 5 day AFEB & pharyngitis; 10 day CAP & sinusitis
- 5 day pack priced at parity to Zithromax; average price per RX shown is after discounts/rebates
- 800M details/year (62% primary, 38% secondary)
- Sampling at parity to current Biaxin levels on basis of courses of therapy sampled
- Peak market share = 6.9% (2009)
- U.S. R&D costs at 60% of total
- NPV does not account for potential cannibalization of Biaxin by ABT-773

**Forecast Update Plan:**

Forecast will be updated if necessary upon receipt of the phase IIIa data 2Q01.

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**C.4.2 Ex-U.S. Sales Forecast** The ex-U.S. sales forecast is shown in Table C.4.2a, below.

Table C.4.2a Ex-U.S. Forecast (Date of Forecast: 8/00)					
	2004	2005	2006	2007	2008
Market (MM packs)*	592	592	593	594	595
- % chg	0.0%	0.0%	0.1%	0.2%	0.2%
Abbott Share (%)	1.1%	2.3%	3.3%	4.3%	4.9%
Abbott packs (MM)	6.5	13.6	19.7	25.3	29.3
Price/Rx (\$)	12.6	12.6	12.6	12.6	12.6
Abbott Sales (\$MM)	82	172	248	321	373
R&D (\$MM)	4	2	2	2	2
SG&A (\$MM)	84	84	84	76	76
SMM (%)	85%	88%	89%	90%	90%
Div. Margin (\$MM)	(19)	63	132	199	254

10 year pre-tax NPV @ 12.5% = \$403MM      10 year pre-tax ENPV @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$234MM      10 year post-tax ENPV @ 12.5% = TBD

\* packs used as a proxy for Rx's (Rx's not audited in most AI markets)

**Key assumptions:**

- Ex-US launch lags U.S. by 6-18 months due to pricing negotiations and/or special registration requirements in AI markets
  - Europe (average): U.S. launch + 6 months = Q1 2004
  - LA (average): U.S. launch + 6 months (Q1 2004)
  - PAA (average): U.S. launch + 1 yr (Q3 2004)
  - Japan (average) = US launch + 1 yr (Q3 2004)
  - Canada = US launch + 12-18 mos (Q3 2004)
- Market is declining approximately 1-2.5% in Europe, Japan and Canada, but increasing approximately 2-3% in LA and PAA
- ABT-773 Pack Price = current Clari price per course of therapy
  - Europe: \$10.8/pack (150mg, 5 day); \$22.6/pack (300mg, 7day avg)
  - LA/Canada: \$13.4/pack (150mg, 5day); \$28.2/pack(300mg, 7 day avg)
  - PAA: \$9.7/pack; \$20.4/pack
  - Japan; \$12.8/pack; \$26.8/pack
- Peak Market share (2008): Europe = 6.0%; LA/Canada = 4.6%; PAA = 3.3%; Japan = 5.9%; 90% of pack share from 150mg QD dose strength
- Dosing = 150mg QID 5 day for bronchitis and pharyngitis; 300mg QID 10 day for CAP and sinusitis
- No resistance claim, however, language in label describing in vitro activity against resistant organisms

**Forecast Update Plan:**

Forecast will be updated by 12/00 after 2001 LRP forecasting cycle, incorporating input from AI affiliates.

### C.5 Facilitating Launch and Market Penetration

There are three components of the strategy to facilitate the launch of ABT-773. These are 1) promotional claims 2) communication strategy 3) opinion leader development. These activities are summarized in these sections below.

#### C.5.1 Desired Promotional Claims

Desired key message	Regulatory requirement	Measure	Timing	Study Number	Type of message	Probability	Share Impact	Comments/Risk
Low potential for resistance development	TRD	Mutation frequency, sub-MIC serial passages, mutation prevention concentration	In progress	Multiple	In-vitro (implied efficacy)	Medium	Med	
Does not induce macrolide resistance	EBD	Ribosome kinetics, MIC evaluations	In progress	Multiple	In-vitro (implied efficacy)	Medium	Med	
Clinic against penicillin/mac resistant S. pneumo	> 15 resistant isolates, high erad. rate	Patient isolates, erad rate (CAP)	5/2002	Phase III studies	Efficacy	Low	Med	
Lower resource utilization vs comparators	2 clinical studies	Overall disease cost	5/2002	Phase III studies	Economic	Low	Med	
Comparable cure/recidivation rates to phase III comparators	Clinical studies	cure/erad rate	5/2002	Phase III studies	Efficacy	Medium	High	
Comparable safety/AE profile to phase III comparators	Clinical studies	safety/AE rate and severity, dropout rate	5/2002	Phase III studies	Efficacy	Medium	High	

#### C.5.2 Communication Strategy

Following is a summary of the activities to date relating to communication strategy:

- 83 posters have been presented at 8 scientific conferences between 1998-2000
- 8 journal articles have been published in two journals, all published in 2000
- Approximately 72 research studies have been completed, many with the intent to publish
- Approximately 87 research studies are in progress, many with the intent to publish
- Approximately 120 external investigators have completed or are in progress with research studies, many with the intent to publish

Much of the above work has dealt with microbiological and/or animal model data. As the compound moves forward, emphasis will shift to the release of more clinically relevant data. Scientific meetings and journals will continue to serve as the primary channels for dissemination of information, though more specialized communication (symposia, advisories, press releases, etc) will start to be used as a more complete understanding of ABT-773 is gained.

An additional focus of study/communication will be towards capitalizing on the unique ribosome binding properties of the product. Information gained from this initiative may be called upon in defense of the selection of the relatively low 150 mg dose. It may also serve as a means of differentiating the product. Various internal and external investigators are working to gain a greater understanding of the underlying science as well as the properties of ABT-773 in this area. Early in 2001 an internal/external "working group" will be convened to develop a strategy for further study in this area and for the optimal dissemination of this data.

Management of all aspects of the ABT-773 communication plan will be facilitated via an intranet tool currently in development by IM&T and external developers. The completion is targeted for November 2000.

### **C.5.3 Opinion Leader Development**

An ABT-773 advisory board of external opinion leaders has been established and has been convened several times over the last several years. The purpose of these advisories has been to solicit guidance for the development of ABT-773 as well as to positively influence their perception of the ketolide class and ABT-773 in particular. An additional mechanism for opinion leader development has been their involvement in both clinical and non-clinical studies. Approximately 120 external investigators, many regarded as top-tier opinion leaders, have experience with ABT-773. A major initiative as ABT-773 moves forward is to identify key national opinion leaders who have favorable experience/opinion of ABT-773 and to work with them to develop an advocacy strategy for publications, scientific meetings, symposia, and advisories.

## D. Regulatory Strategy

### D.1 Regulatory Strategy SWOT Analysis

Table D.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<ul style="list-style-type: none"> <li>QD dosing may be viewed as positive for patient compliance if data is strong</li> <li>If the drug has a favorable risk benefit ratio with added value compared to existing therapies then the likelihood of approvability is high in EU countries or other countries requiring a CPMP package</li> <li>ABT-773 may present a key point of differentiation with promising activity against macrolide and penicillin resistant <i>Streptococcus pneumoniae</i> and enhanced antibacterial activity <i>in vitro</i>. If proven <i>in vivo</i>, this may indicate favourable relative therapeutic value required for approval and inclusion within local use guidelines.</li> </ul> <p>For COFs countries, if the US or EU receives approval then approvals in these LA/PAA countries are assured assuming appropriate sourcing.</p>	<p>Make sure PK/PD data is available to support dose selection rationale</p> <p>The development programs must be designed to unequivocally demonstrate the existence of an added value (e.g. safety or clinical efficacy against resistance species)</p> <p>To utilize the enhanced bacterial activity as a key point of differentiation need to:</p> <ul style="list-style-type: none"> <li>Ensure clinical program is designed to optimize chances of obtaining desired isolates</li> <li>Ensure appropriate pk/pd studies are performed</li> <li>Seek agreement from FDA regarding burden of proof for labeled indication against resistant pathogens</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>Take with food labeling is required to reduce AEs</li> <li>If BID is chosen for either CAP or ABS, diurnal variation may become an issue during FDA review</li> <li>Conformance to Abbott's &amp; FDA's Electronic Document Management System requirements may impact filing date</li> <li>High COG's for bulk drug driving vendor matrix and push to redefine starting material</li> </ul> <p>Harmonization of global clinical trial designs and</p>	<p>FDA will still require pivotal bioavailability studies to be done in fasted state.</p> <p>Justification must be provided</p> <p>Electronic filing likely to be valued very highly by FDA, so need to manage internal process to see that we can meet requirements</p> <p>Need FDA buy-in from End-of-Phase 2 CMC meeting on starting material and vendor matrix, including stability requirements</p> <p>Communicate with team, international affiliates, international experts and</p>

	<p>guidelines</p> <ul style="list-style-type: none"> <li>Differences in medical practice exist worldwide for antibiotics and associated infections</li> <li>Differences in comparator and dosing regimens</li> <li>Stringent EU regulatory environment with antibiotics</li> </ul> <p>EU filing will require a harmonized labeling therefore country-specific favourable labeling cannot be pursued (as done with clarithromycin)</p> <p>Two dose scenario with a lower dose chosen for ABECB, Sinusitis and Pharyngitis with a second dose chosen for CAP may provide limited numbers to assess safety of the higher dose</p> <p>Increased resistance awareness may influence stricter requirements and trend away from lowest effective dose</p>	<p>discuss with EU authorities through agency meetings to ensure design of trials and comparators are acceptable</p> <p>Discuss any country specific issues with authorities, international experts and affiliates. Monitor regulatory environment and competitive products.</p> <p>Discuss issue authorities at agency meeting and ensure MAA addresses this issue. May consider Phase IV studies to address this concern.</p> <p>Ensure clinical program includes relative pk/pd studies and can demonstrate clear efficacy at proposed doses. Ensure clinical program is designed to obtain resistance isolates</p>
<b>Opportunities</b>	<ul style="list-style-type: none"> <li>Labeling for resistant organisms if isolates are obtained</li> </ul> <p>Eligible for Centralised filing process which would provide EU-wide 10 year protection. May also file by Mutual Recognition procedure which more provides flexibility for non-harmonized disease practices (e.g. infectious disease/antibiotics)</p> <p>Once Daily Dosing may enhance compliance</p>	<p>Get agreement with FDA at End of Phase 2 meeting regarding number of isolates required for labeling claim</p> <p>Filing strategy to be determined based on strength of the clinical program and advice received from agencies during planned agency meetings</p>
<b>Threats</b>	<ul style="list-style-type: none"> <li>QT prolongation class labeling in Warnings section of labeling</li> <li>Liver enzyme increases in Warnings section of labeling</li> </ul>	<p>Get agreement with FDA at End of Phase 2 meeting regarding EKG monitoring in Phase 3 and promote theory that QT prolongation is not class related</p> <p>Ensure that non-clinical and clinical program fulfill the CPMP points to consider on QTc prolongation.</p> <p>Ensure that non-clinical and clinical program addresses potential safety</p>

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	<ul style="list-style-type: none"> <li>• Possible failure of short course therapy for Pharyngitis due to more stringent Test of Cure requirement from FDA</li> <li>• If gastrointestinal AEs are high, may affect benefit/risk assessment by FDA</li> <li>• Could be affected by CDC push to reduce antibiotic use; reserve use of drugs effective vs resistant organisms until existing therapies have failed</li> </ul>	labeling issues and MAA/NDA addresses these concerns.
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### Registration Strategy and Timelines for Filing

Table D.2 Registration Strategy and Timelines for Submission		
REGION	Proposed Submission Date	Justification
US	August 2002	Estimated completion of the clinical program and CMC stability data
<b>Europe</b> Filing procedure (Centralised or MRP) to be determined based on strength of clinical data and discussion with authorities	August 2002	Estimated completion of the chemistry/pharmacy and clinical data
<b>Japan</b> Plan to bridge to US data assuming pk profile is similar in Japanese subjects and a successful Phase II bridging study is possible in Japan	TBD, after completion of Phase I local study in Japan.	Bridging obviates the need for a lengthy and expensive Japanese Phase III program. Requires Kiko agreement.

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**D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program**

<b>Table D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program</b>				
<b>COUNTRY</b>	<b>Guideline Requirement</b>	<b>Probability of Achieving</b>	<b>Impact on Filing</b>	<b>Impact on Approvability</b>
<b>US</b>	• Draft Anti-Infective Guidances for CAP, ABPCB, ABS & Pharyngitis	High	High	High
	• Draft Anti-Infective Guidances - General Considerations for Clinical Trials	High	High	High
	• Anti-Infective Points to Consider document	High	High	High
	• ICH Efficacy Guidances – E1 through E12	High	High	High
	• ICH Safety Guidances – S1 through S7	High	High	High
	• ICH Quality Guidances – Q1 through Q7	High	High	High
<b>Europe</b>	All ICH guidelines as above, plus CPMP points to consider on QT prolongation CPMP guideline on the clinical evaluation of antibacterials DRAFT CPMP guideline for pk/pd	High/Moderate	High	High
<b>Japan</b>	All ICH guidelines as above plus local guidelines/JP issues, ICH E5 ethnic bridging guideline.	Moderate/Unknown	High	High



**D.4 Table of Proposed Discussions with Health Authorities**

<b>Table D.4 Table of Proposed Discussions with Health Authorities</b>		
<b>COUNTRY</b>	<b>Reason for Discussion</b>	<b>Proposed timing for Discussion</b>
<b>US</b>	<ul style="list-style-type: none"> <li>• End of Phase 2 – Clinical</li> <li>• End of Phase 2 – CMC</li> <li>• Pre-NDA – Clinical</li> <li>• Pre NDA – CMC</li> </ul>	10/20/00 TBD TBD TBD
<b>Europe</b>	<ul style="list-style-type: none"> <li>• Individual agency meetings with UK, Germany, France and Spain to discuss Phase III Clinical program trial designs</li> <li>• Pre-filing meetings to be determined based on filing strategy</li> </ul>	UK complete – 07/10/00 Germany complete- 07/21/00 France scheduled – 08/30/00 Spain – to be determined
<b>Japan</b>	<ul style="list-style-type: none"> <li>• KIKO- discuss bridging strategy to 300 mg EU/US program</li> <li>• KIKO – re-discuss dose justification</li> </ul>	Complete June 2000 TBD

## E. Development Cost and Sensitivity Analysis

### E.1 Strategic Spending Overview

The tables below describe the major milestones for the ABT-773 Tablet program as well as the Phase II/III studies and associated costs.

Metrics Dates	
Description	Date
DDC Meeting	3/1997
Start of first GLP animal tox study	6/1997
First dose in human (beg. Phase I)	12/1997
First dose in patient (beg. Phase II)	9/1999
First dose in Phase III	11/2000
Last Patient/Last Visit	4/2002
NDA Filing	8/2002
NDA Approval	8/2003
Europe (EMEA) Filing	8/2002
Europe (EMEA) Approval	8/2003
Japan Filing	TBD
Japan Approval	TBD

Protocol # - Study Name	Start (1 <sup>st</sup> Pt)	End (Last CRF)	R/OSS \$000	Total Target Patients	Actual Enrollment
M99-048, Phase II Dose Ranging, ABECB	9/1/99	3/31/00	3,885	300	384
M99-053, Phase II Dose Ranging, Sinusitis	9/1/99	4/30/00	3,172	300	292
M99-054, Phase II Dose Ranging CAP	9/1/99	4/30/00	4,089	300	187
M00-219 Phase III CAP, Dose Ranging	11/7/00	4/30/01	14,400	800	0
M00-216 Phase III ABECB vs Azithromycin US	11/7/00	4/30/01	7,381	600	0
M00-217 Phase III ABECB vs Levofloxacin EUR	11/7/00	4/30/01	4,600	500	0
M00-225 Phase III Sinusitis Dose Ranging	11/7/00	4/30/01	7,200	600	0
M00-223 Phase III Pharyngitis vs Penicillin US	11/7/00	4/30/01	4,340	520	0
M00-222 Phase III Pharyngitis vs Penicillin EUR	11/7/00	4/30/01	5,000	520	0
M00-226 Phase III Sinusitis vs Augmentin US	10/1/01	4/30/02	4,400	450	0
M00-220 Phase III CAP vs Amoxicillin EUR	10/1/01	4/30/02	5,700	500	0
M00-221 Phase III CAP vs Levofloxacin US	10/1/01	4/30/02	8,200	450	0
M00-218 Phase III Sinusitis vs quinolone TBD EUR	10/1/01	4/30/02	5,300	500	0

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**E.2 Base Case Scenario****E.2.a Base Case Scenario for Project:**

	Prior Years	1999	2000	2001	2002	
<b>Base Program</b>						
CMC	17.5	28.6	31.2	22.8	14.5	
- PAR/D/HDC	4.8	5.4	8.6	7.8	4.5	
- SPD	12.7	23.2	22.6	15.0	10.0	
Drug Safety	3.5	2.5	3.4	1.7	1.0	
Other:	7.4	7.7	5.0	4.6	4.0	
Total	28.4	38.8	39.6	29.1	19.5	
<b>Clinical Program</b>						
Registration	2.5	9.5	34.5	61.9	23.3	
Pricing						
Marketing						
Other:						
Total	30.9	48.3	74.1	91.0	42.8	287.1

**E.3 Upside Scenario****Funding Increase**

If funding were to be increased by 25%, how would that increased funding be used?

- 1) Accelerating Program
  - At this point in the program, additional funding will not accelerate the filing any earlier than the August 2002 date. The current program is intense and needs to be accomplished within a short timeframe. Probability of success in the current program is estimated at 50 to 60%.
- 2) Enhancing Program
  - The pediatric and IV formulations are currently not funded and could continue from the earlier work completed in 2000. Approximately \$21MM is required for the IV development and \$39MM for the pediatric development. The IV program would provide support for marketing this antibiotic for serious infections and help the marketing of the tablet, and the pediatric supports the marketing position that this is a safe drug.
- 3) Enhancing Program within Existing Program
  - Additional funding within the current program would allow for additional patient enrollment incentives or an increase in the number of sites participating in the current Phase III program. This would increase the probability of success in achieving the Aug 2002 filing date.

**E.4 Downside Scenario****Funding Decrease**

If funding were to be decreased by, how would that decrease be applied?

- 1) Slowing Program
  - A decrease in program spending would delay the filing of ABT-773 significantly, minimum one year, as RTI indications are seasonal, and the majority of patient enrollment comes from the northern hemisphere.
- 2) Trimming Program
  - Eliminating an indication will cause this filing to be unapprovable as the number of required patients on drug and the four indications being are sought are the minimum RTI indications for approval. The program is only funded currently for one formulation.
  - The current program is currently funded at the minimal acceptable level for approvability by both FDA and AI regulatory agencies.
- 3) Increasing Risk
  - Refer to Item 2 above. Current probability of success for the program is 50 to 60%. Any reduction to the program will significantly delay the filing.



## F. Pharmacokinetics/Pharmacodynamics/Phase 1

### F.1 PK/PD/Phase 1 SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-773 are discussed below:

Table F.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	Phase IIb clinicals and PK/PD data support once daily dosing.	Conduct Phase III for ABECB and pharyngitis at 150mgQD. Further examine 150mgQD for AMS & CAP.
	Food has no influence on ABT-773 PK. High drug levels in alveolar macrophages.	Tolerability may require administration with food. This may explain efficacy vs. <i>H. flu.</i>
Weaknesses	ABT-773 may require a total daily dose of 300mg for severe infections.	Examine 150mg BID for AMS & CAP and conduct tissue level studies.
	ABT-773 is metabolized by and inhibits CYP3A; has potential to cause clinically important drug interactions.	Lowest effective dose (150mgQD) may minimize drug interaction potential.
	ABT-773 has low & variable oral bioavailability. Absorption "window" makes ER dosage forms not feasible.	Multiple ER dosage forms tried, none provided adequate bioavailability and true extended release <i>in vivo</i> .
Opportunities	At 300mgQD, ABT-773 inhibits CYP3A, but inhibition is less than 250mgBID clarithromycin.	May wish to repeat midazolam (CYP3A substrate) interaction study at 150mgQD or BID.
Threats	Disappointing ABT-773 tissue levels (especially WBC and ELF). Competition (Ketek <sup>TM</sup> ) reports higher WBC and ELF levels.	Repeat tissue level studies and in the meantime focus on efficacy data.

### F.2 PK/PD (Clinical)

The Phase 1 program consists of pharmacokinetic, special population, interaction and tissue penetration studies as outlined in section F.3. To attempt to design a once daily dosage form with optimal pharmacokinetics, fifteen prototype formulations were developed for the initial investigations of preliminary safety and pharmacokinetics. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen for further development based on

pharmacokinetics, safety, and ease of manufacture. Studies in special populations, drug-drug interaction assessments and tissue penetration evaluations have been conducted with formulation IR-C.

Table F.2.a lists all the completed, planned and proposed PK/PD clinical trials for ABT-773:

Table F.2.a: Clinical PK/PD Trials (Phase I)					
STUDY	POPULATION	OBJECTIVE/PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M99-105	Healthy Adults	PK of ABT-773 in WBC Relative to Plasma	N = 8	Study completed	Poor partitioning of ABT-773 into WBC.
M99-007	Healthy Adults	Compare Concentrations of ABT-773 in BAL & AM to Plasma	N = 43	Study completed	High concentrations of ABT-773 in AM. Relatively low concentrations in ELF.
M99-142	Healthy Adults	Compare Concentrations of ABT-773 in BAL, ELF, AM, CSF & TLT to Plasma	BAL = 50 CSF = 10 TLT = 10	Ongoing	

### F.3 Phase I Overall Summary

#### Pharmacokinetic and Safety Studies:

In the first Phase I study (M97-716), the pharmacokinetics and safety of ABT-773 (IR-A) were assessed following rising single oral doses (100 – 1200 mg). This study was conducted in two parts with Part I consisting of single rising doses under fasting conditions and Part II a food effect assessment at a single dose of 400 mg. The pharmacokinetics of ABT-773 were linear over the 400 mg to 1200 mg dose range. At doses below 400 mg, the pharmacokinetics appeared to be nonlinear, with AUC increasing more than proportionally with dose. More recent data have indicated that safe and effective doses of ABT-773 in patients will likely be below 400 mg/day and that pharmacokinetic nonlinearity will occur at these clinically-relevant doses. The mean half-lives over the 200 – 1200 mg dose range were between 5.3 - 6.7 hours.

Administration of ABT-773 under nonfasting conditions had little or no effect on the pharmacokinetics. The most commonly reported adverse events were taste perversion and/or events related to the gastrointestinal system including abdominal pain, nausea, vomiting and diarrhea. Administration of ABT-773 with food decreased or eliminated the gastrointestinal adverse events but did not affect the incidence of taste perversion.

In the second Phase 1 study (M97-796) the pharmacokinetics and safety of ABT-773 (IR-A) were assessed in a multiple rising dose study. Total daily doses ranging from 200 mg to 1000 mg were administered for seven days. Over the multiple dose range of 200 to 500 mg BID and 200 to 300 mg TID, the pharmacokinetics of ABT-773 appeared to deviate from dose proportionality and time-linearity. The AUCs increased more than proportionally with increasing dose, and accumulation from single- to multiple-dose administration was greater than predicted. At steady state, the half-life ranged between 6.0 and 8.8 hours. ABT-773 pharmacokinetics exhibited diurnal variation, with lower C<sub>max</sub> and AUC values for doses administered in the afternoon or evening than for doses administered in the morning. In groups who were administered total daily doses of  $\geq 600$  mg of ABT-773, the most frequently reported adverse event was taste perversion.

In the third Phase 1 trial (M98-889) the relative tolerability of two doses of ABT-773, 100 mg TID and 200 mg TID, was compared with that of clarithromycin 500 mg BID in 153 healthy volunteers. There were no significant differences between the incidence of adverse events between the three regimens except for taste perversion which occurred in 8% of subjects receiving ABT-773 100 mg TID, 34.6% of subjects receiving ABT-773 200 mg TID and in 37.2% of subjects receiving clarithromycin.

Three Phase 1 trials were performed to compare steady state pharmacokinetics and safety after five days of treatment with various doses of ABT-773 (IR-A); 100 mg TID vs. 200 mg TID (M99-011), 300 mg once daily vs. 200 mg once daily vs. 100 mg TID (M99-016) and 100 mg BID vs. 200 mg BID (M99-018). Over these dose ranges, the pharmacokinetics of ABT-773 deviated from linearity. As seen previously, the AUCs increased more than proportionally with dose.

#### **Bioavailability Studies:**

Two Phase 1 studies (M98-865 and M98-885) were performed to evaluate the pharmacokinetics of 600 mg once daily doses for four extended-release prototypes of ABT-773 (two per study) administered with food for four days in comparison to formulation IR-A. For the four prototypes, plasma concentration profiles were much lower than those produced by the immediate release reference capsule. As a result, none of these prototypes continued in development.



Seven further Phase I trials (studies M99-023, M99-024, M99-025, M99-026, M99-029, M99-035, M99-042) were conducted to evaluate the pharmacokinetics and safety of ten additional ABT-773 prototypes, two immediate release and eight extended release formulations in comparison to the reference formulation (IR-A). All studies had two, three or four period cross-over designs with nonfasting, multiple once daily or BID ABT-773 5-day dosing in healthy volunteers. Pharmacokinetically, none of the extended release prototype formulations had superior bioavailability compared to the immediate release capsule. In addition, an Intelisite® study (M98-992, not included in the data package) investigating the absorption of ABT-773 confirmed that absorption of ABT-773 from the colon is limited. Due to the solubility profile of the drug, the apparent narrow absorption window, and low absorption from the colon, it appears that an extended release formulation is not feasible. Therefore, optimal bioavailability is expected with an immediate-release formulation rather than extended release formulations. Upon review of the preliminary data, the immediate release formulation (IR-C; M99-024) was chosen for further development as it appeared to be the most robust formulation and demonstrated fewer adverse events and drop-outs than IR-B (M99-023).

Additional biopharmaceutics studies will be conducted to characterize the relative bioavailability/bioequivalence and food effect on the final, production-scale tablet formulation proposed for marketing.

Table F.3.a lists all the completed, planned and proposed clinical trials for ABT-773:

Table F.3.a: Clinical Trials (Phase 1)					
STUDY	POPULATION	OBJECTIVE/PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M97-716	Healthy Adults	Rising Single Oral Doses of ABT-773 in Nonfasting and Fasting Subjects	Part 1 = 56 Part 2 = 24	Study complete	ABT-773 PK were nonlinear. Food has no effect on ABT-773 PK
M97-796	Healthy Adults	Rising Multiple Oral Doses of ABT-773	N = 83	Study complete	ABT-773 PK were nonlinear and had diurnal variation. If the final to-be-marketed regimen is QD, FDA may ask an AM vs. PM PK study.
M99-992	Healthy Adults	ABT-773 PK Comparing Oral IR Capsule to Intellisite® Capsule (Targeted Release in Colon)	N = 10	Study completed	ABT-773 is very poorly absorbed from colon.
M99-011	Healthy Males	ABT-773 PK Comparing 100mgBID to 200mgBID	N = 12	Study completed	ABT-773 AUC increased more than proportionally with dose and had diurnal variation.
M99-016	Healthy Males	ABT-773 PK Comparing 300mgQD & 200mgQD to 100mgTID	N = 24	Study completed	ABT-773 AUC increased more than proportionally with dose and greater exposure achieved by QD vs. TID dosing.
M99-018	Healthy Males	ABT-773 PK Comparing 100mgBID to 200mgBID	N = 24	Study completed	ABT-773 AUC increased more than proportionally with dose and had diurnal variation.
M99-024	Healthy Males	ABT-773 PK Comparing 150mg IR C Tablet to 100mg Capsule	N = 18	Study completed	Prototype C tablet was bioequivalent to the reference capsule. Greater exposure achieved by QD vs. BID dosing.

Table F.3.a: Clinical Trials (Phase I) Cont.					
STUDY	POPULATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
Special Population Studies					
TBD	TBD	Effects of Age and Gender on ABT-773 PK		Protocol TBD	ABT-773 clearance may increase with age. Clarithromycin AUC higher in females than in males.
M99-127	Severe Renal Impaired vs. Healthy	Effects of Renal Impairment on ABT-773 PK		Protocol in progress	No effect of renal impairment on ABT-773 PK expected.
M99-119	Healthy Adults	ABT-773 Single and Multiple Dose Ranging PK in Japanese vs. Non-Japanese	N = 84	Study completed	At equal doses, Japanese had about 50% greater plasma ABT-773 concentrations than non-Japanese. Lower dose needed in Japanese patients.
M99-126	Mild & Moderate Hepatic Impaired vs. Healthy	Effects of Hepatic Impairment on ABT-773 PK	N = 24	Ongoing	

Table F.3.a: Clinical Trials (Phase 1) Cont.					
STUDY	POPULATION	OBJECTIVE/ PURPOSE OF STUDY	# OF PATIENTS	FUNDED?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
<b>Drug Interaction Studies</b>					
M99-128	Healthy Adult Females	Effects of ABT-773 on the PK of OC's	N = 18	Study completed	No clinically significant drug interaction was observed.
M99-138	Healthy Adults	Effects of Ketoconazole (CYP3A inhibitor) on PK of ABT-773	N = 18	Study completed	Ketoconazole inhibited ABT-773 metabolism increasing ABT-773 AUC >5 times.
M99-139	Healthy Adults	Effects of ABT-773 on the PK of Theophylline	N = 18	Study completed	No clinically significant drug interaction was observed.
M00-155	Healthy Adults	Effects of ABT-773 on the PK of Midazolam (CYP3A substrate)	N = 24	Study completed	ABT-773 inhibited midazolam metabolism doubling midazolam AUC. Interaction smaller than interaction between clarithromycin and midazolam.
M00-156	Healthy Adults	Effects of Rifampin (CYP3A inducer) on PK of ABT-773	N = 18	Study completed	Rifampin induced ABT-773 metabolism decreasing ABT-773 AUC by >90%. ABT-773 should not be given with any drug that might induce CYP3A.
TBD	Healthy Adults	Assessment of the Pharmacokinetic Interaction Between ABT-773 and Warfarin	TBD	Protocol TBD	R-warfarin is a CYP3A substrate and warfarin is a NTI drug.
TBD	Healthy Adults	Assessment of the Pharmacokinetic Interaction Between ABT-773 and Digoxin	TBD	Protocol TBD	Digoxin is a Pgp substrate and a NTI drug.

#### Drug Interaction Program

As indicated in the Phase 1 clinical overview, further studies in special populations and drug-drug interaction assessments will be conducted. Preliminary pharmacokinetic data are available from five drug interaction studies. Because ABT-773 will be administered to women who rely upon oral contraceptives for birth control, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of the components of a commonly-used combination oral contraceptive product (Ortho-Novum 1/35). Because ABT-773 will be co-administered with

theophylline in bronchitis patients, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of theophylline. Because ABT-773 is known to be a substrate and inhibitor of the cytochrome P450 3A4 isoform subfamily (CYP3A4) in vitro, three clinical drug-drug interaction studies suggested in FDA Guidance on in vivo drug metabolism/drug interaction were conducted. Because ABT-773 is a CYP3A4 substrate, we have examined the effects of the CYP3A4 inhibitor, ketoconazole, and the inducer, rifampin, on the pharmacokinetics of ABT-773. Because ABT-773 may be an inhibitor of CYP3A4 in vivo, we have examined the effects of ABT-773 on midazolam pharmacokinetics. Preliminary pharmacokinetic and safety data are also available from a special population study in Japanese subjects.

In addition to these five completed drug-drug interaction studies, the effects of ABT-773 on the pharmacokinetics of warfarin and digoxin will be examined. A special population study to examine the effects of mild and moderate hepatic impairment (Child-Pugh) on ABT-773 is ongoing. Because no more than 10% of ABT-773 is excreted in the urine, a reduced-design study to examine the effects of severe renal impairment (creatinine clearance: 10-29 ml/min) on ABT-773 will be conducted. An additional special population study will be conducted to examine the effects of age and gender on ABT-773 pharmacokinetics.

## G. Clinical Trial Program

### G.1 Clinical Trial Program SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-XXX are discussed below:

Table G.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
<b>Strengths</b>	<ol style="list-style-type: none"> <li>150 mg QD dose should minimize side effects and provide sufficient exposure for efficacy.</li> <li>Complete Pharyngitis, and ABECB comparative Phase III studies by 2Q, 2001, and concentrate thereafter on CAP and ABS.</li> </ol>	<ol style="list-style-type: none"> <li>Two studies using this dose, two studies comparing it to higher dose for further evaluation in CAP and sinusitis.</li> <li>Prepare all documentation for NDA/regulatory filings before CAP and sinusitis studies complete.</li> </ol>
<b>Weaknesses</b>	<ol style="list-style-type: none"> <li>AE profile - GI, taste, at 300mg significantly higher than clarit 500mg BID.</li> <li>Completion of CAP and sinusitis studies comparing 150 QD and BID may not occur by 2Q, 2001, delaying start of other pivotal studies.</li> <li>Further changes/amendments to protocols.</li> <li>Fail to enroll CAP and sinusitis patients early in season for Phase III trials starting 3Q, 2001.</li> </ol>	<ol style="list-style-type: none"> <li>Use lower dose (150 mg QD).</li> <li>Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Monitor data carefully and stop study if significant trend towards one arm.</li> <li>Amendments will not be finalized until studies are initiated with original protocols.</li> <li>Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Add South American sites if needed (2002).</li> </ol>
<b>Opportunities</b>	<ul style="list-style-type: none"> <li>Claim for resistant organisms.</li> </ul>	<ul style="list-style-type: none"> <li>Conduct studies in geographical locations where resistant bacteria are prevalent. Use central labs wherever possible.</li> </ul>
<b>Threats</b>	<ul style="list-style-type: none"> <li>Studies being done by other sponsors.</li> </ul>	<ul style="list-style-type: none"> <li>Pay appropriately; maximize contact with investigators. Hold successful investigator meetings and use retainer fees if necessary.</li> </ul>

## G.2 Clinical Trials

Table G.2.a lists all the planned and proposed clinical trials for ABT-773:

Table G.2.a: Clinical Trials (Phase 2-3)					
STUDY	PHASE	OBJECTIVE/ PURPOSE OF STUDY	# OF PTS	FUNDED ?	LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS
M00-219	III	CAP; 773 150 QD vs. 150 BID	800	Yes	11/2000 - 4/2001, 50% likely to finish on time.
M00-216	III	ABECB; comparing AZI vs. 773	600	Yes	11/2000 - 4/2001, 100% likely to finish on time.
M00-217	III	ABECB; comparing Levo vs. 773	500	Yes	11/2000 - 4/2001, 100% likely to finish on time.
M00-225	III	Sinusitis; 773 150 QD vs. 150 BID	600	Yes	11/2000 - 4/2001, 50% likely to finish on time.
M00-223	III	Pharyngitis; comparing penicillin (250 mg TID) vs. ABT773	520	Yes	11/2000 - 4/2001, 100% likely to finish on time. There is some chance that it will not meet FDA standards of >85% at 30 days.
M00-222	III	Pharyngitis; comparing penicillin (500 mg TID) vs. ABT773	520	Yes	11/2000 - 4/2001, 100% likely to finish on time.
M00-221	III	CAP; comparing Levo vs. 773	450	Yes	09/2001 - 04/2002, 50% likely to finish on time.
M00-220	III	CAP; comparing Amoxicillin vs. 773	500	Yes	09/2001 - 04/2002, 50% likely to finish on time.
M00-226	III	Sinusitis; comparing quinolone TBD vs. 773	450	Yes	09/2001 - 04/2002, 75% likely to finish on time
M00-218	III	Sinusitis; comparing Augmentin vs. 773	500	Yes	09/2001 - 04/2002, 75% likely to finish on time

### Phase 2

In Phase 2a study M98-967, subjects with ABECB were treated with 100 mg TID or 200 mg TID dosing regimens which resulted in high clinical and bacteriological cure rates (see Section 9.3).

Three Phase 2b studies (see Section 9.4) conducted in both the US and EU investigating ABT-773 once daily doses have been completed:

- M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days)
- M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days)
- M99-048 - Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)

### Phase 3

The Phase 3 program consists of trials originating in either the United States or Europe comparing the safety and efficacy of ABT-773 in the proposed indications as described below.

- Community Acquired Pneumonia (total n ~ 1200 for ABT-773 arms)
  - M00-221 - One pivotal United States Phase 3, Controlled Study
  - M00-219 - One pivotal United States Phase 3, 2 Dose Study
  - M00-220 - One supportive European Phase 3, Controlled Study
- Acute Bacterial Exacerbation of Chronic Bronchitis (total n ~ 500 for ABT-773 arms)
  - M00-216 - One pivotal United States Phase 3, Controlled Study
  - M00-217 - One supportive European Phase 3, Controlled Study
- Acute bacterial sinusitis (total n ~ 1000 for ABT-773 arms)
  - M00-226 - One pivotal United States Phase 3, Controlled Study
  - M00-225 - One pivotal United States Phase 3, 2 Dose Study
  - M00-218 - One supportive European Phase 3, Controlled Study
- Pharyngitis (total n ~ 500 for ABT-773 arms)
  - M00-223 - One pivotal United States Phase 3, Controlled Study
  - M00-222 - One supportive European Phase 3, Controlled Study

### Strategy of Clinical Program

A global clinical development program has been implemented intended for world-wide registration. An estimated total of 5,500 subjects will be enrolled in the Phase 3 clinical program including both study drug and comparator. Approximately 3,500 subjects world-wide will be available for the efficacy evaluation of ABT-773. An estimated total of 5,300 subjects will be available for the safety evaluation of ABT-773 including Phase 1/2/3 data.

#### 1. ABT-773 Dose Selection for Phase 2a Study in ABECB (M98-967)

ABT-773 is a potent antibacterial agent with *in-vitro* activity against community-acquired respiratory pathogens including *S. pneumoniae*, (including penicillin-resistant and macrolide-resistant strains; PRSP and MRSP) *H. influenzae*, *S. pyogenes*, *M. catarrhalis* and atypical organisms including *Mycoplasma spp.*, *Chlamydia spp.* and *Legionella spp.* It also has activity against anaerobic gram-positive bacteria found in the normal upper respiratory tract and the bowel flora.



In addition, ABT 773 has been shown to demonstrate *in vivo* efficacy in animal model pulmonary infection studies against these prevalent respiratory pathogens.

The highest MIC exhibited to ABT-773 among respiratory pathogens (including PRSP/MRSP) is that of *H. influenzae*. The MIC<sub>90</sub> ranges from 2-4 µg/ml. In rat lung efficacy studies the CFU reduction in rat lung ( $2 \log_{10}$  -  $3 \log_{10}$ ) was exhibited by an AUC of 2.4-9.4 µg•hr/ml when the drug was administered as a BID regimen.

Unformulated drug was delivered in capsules as QID, BID and TID regimens in dose-escalating single and multiple dose studies (100 mg QD as lowest dose) in order to evaluate the PK properties and safety profile, and to determine the dose regimen for the Phase 2a study.

The three key factors considered in selecting the dose and frequency of dosing for the Phase 2a study from the Phase 1 dose-escalating studies were; the AUC range necessary to treat *H. influenzae* in animal model studies, the safety profile of the drug, and the goal to simulate an extended release profile for eventual once daily dosing.

Based on these considerations 100 mg TID and 200 mg TID dose regimens were selected for Phase 2a study M98-967. The mean AUCs for these regimens determined in Phase 1 studies were approximately 4.1 µg•hr/ml and 14.9 µg•hr/ml, respectively.

## **2. Dose Selection for Phase 2b Studies ABECB (M98-048), ABS (M98-053) and CAP (M98-054)**

In several Phase 1 studies the mean AUC for 300 mg QD (3 x 100 mg capsules) ranged from 4.8-8.0 µg•hr/ml. The mean AUC values for the QD regimen were higher in all four Phase 1 studies than for TID regimen, and additionally, in one Phase 1 cross-over study (5.9 vs. 4.1 µg•hr/ml) due to some extent of diurnal variation in absorption.

The efficacy/safety results of 100 mg TID (M98-967) were excellent. The clinical and bacteriological cure rates were both 98% and adverse events were low with the exception of 11% diarrhea. The study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Pharmacokinetic data from a subset of subjects in this study indicated that the mean AUC for this regimen was 5.5 µg•hr/ml. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patient compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen (plasma mean AUC values of 4.1 and 5.9 µg•hr/ml, respectively) as discussed

above. In addition, the 300 mg dose administered QD had a mean  $C_{max}$  value of 0.9 µg/ml, which together with the exposure outlined above, provides adequate coverage for bactericidal activity against PRSP/MRSP with MIC<sub>90</sub> of 0.12.

Phase 2b studies were initiated with an immediate release tablet after multiple prototype extended release tablets failed to yield AUC values similar to that of the immediate release capsule and did not exhibit the desired extended release profile. Therefore, 150 mg immediate release tablets were manufactured and demonstrated to be bioequivalent to capsules (150 mg x 2 tablets vs 100 mg x 3 capsules) and were used in all three Phase 2b studies.

The 300 mg QD middle dose was bracketed in two of the dose-ranging Phase 2b studies (ABECB and ABS) with 150 mg and 600 mg doses to explore the optimal efficacy and safety range of the drug. In CAP, only 300 mg and 600 mg QD doses were used.

### 3. Dose Selection for Phase 3 Studies

The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABECB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.

The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.

Overall eradication of *S. pneumoniae* was excellent in all three studies. The data suggested that there was no apparent relationship between MIC and eradication or persistence of the isolates in the three trials, as would be expected with a susceptible population. There were no significant differences in eradication of *S. pneumoniae* between the dose groups in each of the trials and no evidence of development of resistance or of an increase in MIC in persistent isolates. Four MRSP isolates (2 mef/2 erm) were eradicated at the 150 mg dose in the ABECB study.

Regarding *H. influenzae*, overall eradication rates were high in ABECB and CAP. There were too few isolates in ABS to draw any conclusions. The data suggested that eradication or persistence was not predicted by the MIC value again consistent with a susceptible population where occasional persistent isolates are seen. Differences in eradication of *H. influenzae* were not significant between the dose groups in the three studies. For *H. influenzae*, 17/18 (94%) isolates were presumed eradicated in the ABECB study in the 150 mg arm of the study. The number of

*H. influenzae* isolates in the ABS study were too few to reach a meaningful conclusion (3/5) of presumed eradication.

There were no statistically significant differences between the 150 mg and 300 mg arms of the clinical outcome in ABECB and ABS studies, and the confidence intervals suggested they were equivalent in clinical outcome. However, 150 mg was tolerated better as far as taste disturbance and GI adverse events.

ABECB/Pharyngitis - Since both confidence intervals and statistical tests suggested that 150 mg and 300 mg dose groups were similar in both clinical and bacteriological outcome, it was decided to proceed into Phase 3 for ABECB indication with two studies using a 150 mg QD dose for 5 days. It was also decided to use this dose in the pharyngitis/tonsillitis studies, based on excellent *in vitro* activity of this drug against *S. pyogenes*, including macrolide resistant strains.

ABS - Excellent clinical activity was demonstrated in the 150 mg arm. Due to low pathogen recovery rate in this study, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID (with sinus punctures) in lieu of the open single dose Phase 3 study as recommended in the FDA guidance document. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed. For this first study, 150 mg BID was selected since this regimen has been shown to have a lower  $C_{max}$  compared to 300 mg QD, thus potentially resulting in less taste disturbance and possibly lower GI side effects. In addition, the AUC values (3.9-5.8) obtained in Phase 1 studies are within AUC values of 150 mg and 300 mg QD, two doses that were shown to be effective in this indication.

CAP - For this indication, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID in lieu of the open single dose Phase 3 study as recommended in the guidance document. The 150 mg QD dose was included, although it was not evaluated in the Phase 2b study, it exhibited efficacy in the ABECB and ABS Phase 2b studies. The 150 mg BID was selected due to its potentially lower taste disturbance and GI adverse event profile compared to 300 mg QD. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed.

#### 4. Selection of comparators for Phase III studies

Selection of comparators were based on input from PPD, AI and affiliate marketing groups, medical and regulatory members of PPD and AI and finally input from three regulatory agencies

in Europe (UK, France and Germany) as well as US FDA Anti-Infective Division. A total of 10 studies are planned to be conducted. Two studies in ABECB, one in Europe and one in US. The European study will be vs Levofloxacin and US study vs Azithromycin. Both drugs have major market shares in this indication, Azithromycin in US and Levofloxacin is gaining momentum in Europe.

There are three planned studies for ABS, including two comparative studies vs Augmentin. And the two dose ABT 773 study. Augmentin is a key product in this indication both in US and Europe. In all probability, for the European study, Augmentin will be replaced with a quinolone. The plan will be finalized shortly.

The plan for acute streptococcal pharyngitis (ASP) calls for two studies against the standard treatment ; Penicillin V. 500mg tid, one in US and the second in Europe.

The CAP plan calls for three studies, the first, a two dose study of ABT 773 followed by a comparative study in Europe vs Augmentin and a comparative study in US vs Levofloxacin. Both products are used in this indication and it will be important to compare the efficacy/safety profile of ABT 773 with these agents. In all probability, for the European study, Augmentin will be replaced with a Amoxicillin 1gm TID. The plan will be finalized shortly

## H. Chemistry, Manufacturing and Controls

### H.1 Chemistry, Manufacturing and Controls SWOT Analysis

Table H.1 SWOT analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	Over 3600 kg of bulk drug have been successfully manufactured with overall yields improving from 21% to greater than 30%. Excellent progress on improving costs of bulk drug, currently less than \$6500/kg with target of \$2500/kg at launch.	Produce required development quantities of bulk drug to meet the cost targets at launch. Continue to obtain yield improvements through process work and manufacturing volume.
	Registration runs incorporated qualifying vendors for intermediates that will drive further bulk drug cost reductions and assure availability of bulk drug.	Obtain Regulatory approval (both AI and FDA) to identify intermediate step 5 as a starting material to allow for further process improvements at the earlier steps of manufacturing.
	Formulation is a familiar technology, immediate release QD formulation manufactured by wet granulation.	Continue to decrease cost of intermediates through use of three to four vendors.
	Two sites of final product manufacturing (one in the U.S. and one in AI) at launch.	Utilize an integrated scale-up program with both PARD and IDC to assure that a single formula/process will be used worldwide.
Weaknesses	Current bulk drug process requires 9 steps and high cost side chain which may limit potential cost improvements beyond launch.	Two manufacturing sites provides back up support to AI and future potential back up to the U.S.
	ABT-773 has a bitter after taste as a result of excretion into the saliva that cannot be masked in the formulation. This is the most frequent adverse event identified in the Phase II clinicals.	Process development underway to evaluate optimized/new chemistry routes and potential to simplify the manufacturing process.
	Phase III clinicals and NDA stability will be performed using an intermediate scale formulation.	The 150 mg tablet minimizes after taste problems however, this will be a challenge in formulating a pediatric product.
Opportunities	Due to Regulatory issues, there will not be a back-up site for the U.S. at launch.	A bioequivalency study will be performed linking the 10L bench formulation used in the Phase II clinicals, to the 300L intermediate formulation used in the Phase III clinicals, to the commercial scale (1200L U.S. and 600L U.K.) formulations.
	Experience with bulk drug substance in terms of physical properties will allow us to develop specifications to improve consistency in formulation.	Evaluate a separate project to obtain second site approval for the AI site to provide back up to the U.S.
		Particle size analysis is ongoing to provide data to support defining physical specifications by January 2001.

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	Obtaining regulatory approval for definition of step 5 as starting material will provide more opportunity for process improvements to reduce COGs	SPD, PPD and AI are collaborating on a solid data package to defend our step 5 starting material definition. An end of Phase II CMC meeting will be scheduled at the end of 2000 with FDA to discuss our strategy. Early discussions with the U.K. regulatory agency were optimistic.
<b>Threats</b>	Having one site for bulk drug can always carry risks.	A second site (Puerto Rico or Italy) will be considered in 2001 based on marketing forecast and capacity.

## H.2 SPD/PPD Chemical Sciences

SPD has made significant breakthroughs since 1997 to bring the cost of drug from \$30M to \$6.5M. Further reductions are expected by reducing the cost of the PQC side chain (competitive bidding among vendors), reducing the number of process steps, reducing the number of intermediate isolations, and increasing the batch size. An ongoing analysis of the assembly process is being made to evaluate the efficiencies gained in various steps in the process, and/or outsourcing a series of steps. The cost of drug during the filing year, 2002 is anticipated to be about \$2500/Kg.

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**Bulk Drug Requirement**Project: ABT-773 Adult Tablet

Inventory Balance

964kg

End Q4 1999

Bulk Deliveries			Usage (Quantity)			
	Description	Quantity	Clinical	Formulation	Scale-Up	Inventory
Q1 2000	Campaign 6, pre-NDA run	321.2 kg	321.2kg			1285.2kg
Q2 2000	Campaign 7, 8, 9 NDA runs	1008.9 kg			1008.9kg	2294.1
Q3 2000	Campaign 10, NDA run, Cam 11,12 dev runs	1029.9 kg			1029.9 kg	3324kg
Q4 2000	Campaigns 13, 14 development runs	670 kg			670 kg	3994kg
Q1 2001	Campaign 15, 16 development runs	670 kg			670 kg	4664kg
Q2 2001	Shut down for facility upgrade					4664kg
Q3 2001	Campaign 17	335 kg			335 kg	4999kg
Q4 2001	Campaign 18,19	670 kg			670 kg	5669kg

Lead Time (request to delivery; weeks) 6 mo

Comments:

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**Schedule B ABT-773 Bulk Drug Usage – Tablet Formulation**

<b>Task</b>	<b>Start</b>	<b>Finish</b>	<b>Task Use</b>
1 10L Formulation Prototypes	Nov/09/98	Jun/30/99	107.8
12 75L Process Dev't/Bulk Drug Eval (24 runs, 200 kg)	Aug/23/99	Oct/01/99	151.0
Clinical Re-Supply PH II	Sep/08/99	Sep/08/99	5.4
14 Dissoln Method Justification Biostudy- Clin Mfg - 3 runs	Oct/04/99	Nov/15/99	24.0
16 Process Dev/Bulk Drug Eval 75L Pt2 (8 runs, 66.4 kg)	Nov/16/99	Dec/10/99	59.0
18 UK Site/2nd Process Verification 25L (33 kg)			
Batches 1-3	Dec/01/99	Jan/31/00	10.0
Batches 4-6	Feb/01/00	Mar/13/00	10.0
Batches 7-10 (two batches)	Mar/14/00	Oct/11/00	13.2
22 Proc. Supportive Dev, 75L Pt3 (16 runs-rep, Scale; 132.8kg)	Dec/13/99	Feb/04/00	132.8
24 75 L Bulk Drug Eval Pt 3 (10 runs; INCL cmpn 6 re-work)	Feb/01/00	Dec/01/00	84.7
26 Process Dev 300L (4 runs; 133.2 kg)	Jan/10/00	Feb/04/00	130.0
Phase III Clin Supply mfg, 75L Gral, 300 mg white, 62-329-AR	Mar/14/00	Mar/21/00	16.1
75L, 200 mg IR-D, lot 65-362-AR	May/22/2000	Jul/14/2000	24.1
28 Process Dev Pre-NDA (11 runs; 366.3 kg)	Feb/07/00	Apr/14/00	364.0
300L Gral, 300 mg IR-D ScaleUp Lot: 65-015-4Q	May/31/2000	Jun/13/2000	64.2
150 mg switch			
150 mg factorial compression study			24.0
150 mg tablet coating study			56.0
33 Mfg. NDA Runs - 1 Strength (4 lots/10 runs; 333kg)			
34 NDA Lot 1 (Abbott; Cmpgn 7-rework)	?	Jul/17/00	66.6
NDA Bio Lot 2 (ChemiSpa), Phase III supplies; 66-018-4Q	Jul/31/00	Aug/11/00	66.6
NDA Lot 3 (Uquifa); 67-021-4Q	Sep/25/00	Oct/06/00	66.6
NDA Lot 4 (Taisho)	Sep/25/00	Oct/06/00	66.6
39 Process Verification 65 L (146 kg)	Feb/07/00	Sep/29/00	
Batches 1-6	Oct/18/00	May/31/00	50.0
Batches 7-12	Jun/01/00	Jul/31/00	50.0
Batches 12-15 (two batches)	Aug/01/00	Mar/26/01	35.0
Biobatch, 65L vs 300L (20 kg)	May/01/01	May/31/01	20.0
46 Process Dev 1200 L (4 runs, 532 kg) +1 run?= 665kg	Jan/22/01	Mar/05/01	665.0

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50	1200L Def Bio & Registration Lots (3 lots, 4 runs; 532 kg)	Mar/06/01	Jul/09/01	532.0
	Definitive Biostudy, 300L vs 1200L	May/29/01	Jun/25/01	
57	75L Supportive Dev (For the 1200L, 20 runs; 166 kg)	Jan/17/01	Aug/23/01	166.2
58	300L Supportive Dev (For the 1200L, 5 runs; 166.5 kg)	Jan/17/01	Aug/23/01	167.0
60	Demonstration Lot 1200 L (3 runs; 399 kg)	Apr/01/02 ?	Jun/21/02	399.0
65	Process Transfer(i) 600L U.K. Site (3X 83 kg= 249kg)	Apr/19/01	May/18/01	249.0
	Process Transfer (ii) 600L U.K. (2x 83kg= 166 kg)	Jun/27/01	Jul/24/01	166.0
	Bio Batch UK	Sep/13/01	Oct/02/01	83.0
	Batch Analysis, 2 lots; 2x 83 kg	Sep/05/01	Sept/27/01	166.0
	Demo Batch 1 UK; (1 lot, 3 runs= 333 kg)	Apr/04/02	May/03/02	333.0
	1200L Validation Runs (3 Lots, 3 Runs ea; 1197 kg)	Jun/05/02	Aug/28/02	1200.0
	Launch		1Q2003	
	<b>Total Bulk Drug Usage</b>			5823.90

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## Schedule C

**Bulk Drug Cost Status**

	<b>Current Average Cost (000)</b>	<b>Projected Commercial Cost (000)</b>
Materials	3.7	1.3
Labor/Equipment	2.4	1.05
Process Support	0.4	.15
<b>Total</b>	<b>6.5</b>	<b>2.5</b>

<b>Event</b>	<b>Year</b>	<b>Project Average Cost/Kilo</b>	
		<b>DDC</b>	<b>Actual/Projected</b>
DDC	97	150	150
	98	30	30 A
Phase IIb	99	10	10 A
Phase III start	00	7.5	6.7 A
	01	5.0	5.0 P
Filing	02	4.0	4.0 P
Launch	03	2.5	2.5 P
Dose Projection		150mg/Day	150mg/Day
Cost/Dose/Day Bottle		\$0.4218/Day	\$0.4218/Day
Cost/Dose/Day Blister		\$0.5702/Day	\$0.5702/Day

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### **II.3 PARD/IDC**

An immediate release 150 mg formulation has been selected for commercial development of ABT-773. The formulation was reduced in size from the original 300 mg tablet previously targeted for development. The formula and process will be global with respect the excipients and an integrated scale up program with the IDC will assure that a single formula/process (with common packages) will be used throughout the world. The CMC working group continues to review needs on the bulk drug for clinical use and process development as the program develops. Common specifications for the bulk drug substance and the formulation remain a goal of the CMC development group.

### **H.4 Manufacturing**

ABT-773 tablets will be manufactured in AP16 for PPD domestic supply, and as a back-up facility for AI supply. Queenborough, UK will manufacture for AI supply, including Japan. There will be a common, global formula (0.3g tablet weight, with pale pink coating ). The only possible exception will be if we need to develop different codes of bulk drug for PPD and AI.

The manufacturing process is a conventional tableting process. In AP16, ABT-773 will be granulated in the 1200L Gral, in 3 runs, then blended (75 cuft), compressed and coated (60" Accelacoater) as 150mg tablets. In the UK, ABT-773 will be granulated in the 600L TK Fielder, in the 3 runs, then blended and coated as 150mg tablets. The Japanese product will be manufactured with the same granule, to a lower compression weight, if Japan proceeds with 100mg tablets. This strength is yet to be determined. Capacity reviews at both plants indicate that there is sufficient capacity, including upside demand. The tablets will be packaged into 30# bottles, and peelable blister (Hospital Unit Dose) and push-through blister (compliance pac)

### **H.5 Patent Issues**

U.S. Patent 5,866,549 claiming ABT-773 and its analogs issued on February 2, 1999. The patent will expire on September 4, 2016. Three divisional applications claiming related compounds in the series are pending prosecution in the United States Patent and Trademark Office. The patent applications corresponding to the issued patent and pending patent applications have been filed in more than forty countries outside the US, thus providing extensive worldwide patent protection for the compound

## I. Non-Clinical

### I.1 Non-Clinical SWOT Analysis

Strengths, weakness, opportunities and threats regarding the non-clinical program for ABT-773 are discussed below:

Table I.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats)		
CATEGORY	ITEM (Probability/Impact)	STRATEGY
Strengths	<p>All key toxicology studies have been initiated or completed.</p> <p>ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Erm<sup>AM</sup> and Mef phenotypes; it does not induce MLS<sub>B</sub> (macrolides, lincosamides and streptogramin B) resistance.</p>	<p>Complete Tox package for NDA early on.</p> <p>Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.</p>
Weaknesses	<p>Tox: Relatively small safety margins between the no-effect level exposures and clinical exposure.</p> <p>Micro: Pharmacokinetic profile based on traditional profiles, may not support the 150mg dose.</p> <p><i>H. Flu</i> MIC 2-4 is a high MIC to achieve by blood levels.</p>	<p>Safety data is available from clinical studies.</p> <p>Ribosome kinetics are now being studied as a means of providing crucial support to our decision to proceed with 150 mg. A plan has been established to devise a mechanistic rationale for the 150 mg program that goes beyond the traditional two-factor paradigm i.e. concentration &amp; MIC and establishes this concept as the new in vitro paradigm to predict efficacy.</p> <p>Demonstrate clinical activity in <i>H. flu</i> and use tissue level data if available.</p>
Opportunities	<p>Micro: Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes</p>	<p>Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.</p>
Threats	<p>Testicular effects and impaired fertility in the rat Segment I study.</p>	<p>Fertility evaluation should be included in the clinical program.</p>

## I.2 Toxicology

All key toxicology studies for ABT-773 have been initiated or completed. All acute and genetic toxicity studies, two-week toxicity studies in rat and monkey, one-month toxicity studies in rat and monkey, a three-month study in rat, and embryonic and fetal developmental (Segment II) studies have been completed. A three-month study in monkey, a juvenile toxicity study in rat, a fertility and early embryonic development (Segment I) study in rat, a peri- and postnatal (Segment III) study in rat and an antigenicity study in guinea pig are ongoing.

In rats, increased mortality, decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, lung, testes and epididymides were observed at dosages of 180 and 160 mg/kg/day in the one-month and three-month study, respectively. Mild and reversible toxicity of these organ systems was seen at 60 mg/kg/day. The no-toxic-effect level (NTEL) in the three-month rat study was 20 mg/kg/day ( $AUC = 11-25 \mu\text{g}\cdot\text{hr}/\text{ml}$ ). The mean plasma exposure of ABT-773 in humans is expected to be  $2-5 \mu\text{g}\cdot\text{hr}/\text{ml}$  (150-300 mg/day dose) and thus the NTEL in animals are approximately 2-13 times higher than anticipated human exposures.

In monkeys, emesis was observed in a dose-related manner. Decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, bone marrow and lymphoid tissues were observed at a dosage of 200/140 mg/kg/day in the one-month study. Preliminary data showed that liver toxicity was also observed at dosages of 50 and 100 mg/kg/day in the three-month study. The no-toxic-effect level (NTEL) in the three-month monkey study was 25 mg/kg/day ( $AUC = 7-10 \mu\text{g}\cdot\text{hr}/\text{ml}$ ); exposures at this dosage are approximately 1.5-5 times higher than anticipated human exposures.

Embryonic and fetal developmental studies conducted showed no fetal malformation at dosages up to 80 mg/kg/day in rats and 100 mg/kg/day in rabbits. In an ongoing fertility and early embryonic development study, preliminary data showed adverse effects on fertility at dosages of 60 and 180 mg/kg/day. Recovery of this effect on fertility was seen at 60 mg/kg/day, but not at 180 mg/kg/day. This finding agrees with the testicular effects seen in the three-month rat study. Clinical implications of this finding is not known, although similar findings have been reported with other macrolides. Preliminary data of the peri- and postnatal study showed decreased pup growth and development at 80 mg/kg/day; these effects were believed to be secondary to reduced weight gain of dams during gestation.

Genetic toxicology studies conducted with ABT-773 included Ames assay, mouse lymphoma assay, *in vitro* cytogenetics assay and *in vivo* mouse micronucleus assay. ABT-773 was not found to be genotoxic in any of these assays.

New impurities, not covered by the toxicology lot used for three-month studies, have been generated. Acute toxicity, genotoxicity and bioavailability studies are being conducted with these impurities to qualify their use in the clinical trials. Longer term toxicology testing will be done when the impurity profile for ABT-773 is determined (NDA runs).

### 1.3 Metabolism

Studies of the oral or intravenous single dose pharmacokinetics of ABT-773 have been performed in the rat, mouse, dog and monkey following single doses. These data suggested ABT-773 may possess a balanced pharmacokinetic profile similar to that of clarithromycin. ABT-773 exhibits sufficient plasma concentrations and tissue distribution to provide effective treatment *in vivo* for bacterial infections of upper and lower respiratory tract. The data from the study in dogs indicate that ABT-773 has a favorable oral pharmacokinetic profile with 51.3% absolute bioavailability from a simple capsule formulation and low animal-to-animal variability. ABT-773 has a half-life similar to that of clarithromycin in dogs (4.1 and 5.4 hrs, respectively), with a  $C_{max}$  of 0.88  $\mu\text{g/mL}$  following an oral dose of 5 mg/kg.

[ $^{14}\text{C}$ ] ABT-773 was found to undergo NADPH-dependent metabolism by liver microsomes from mouse, rat, dog, monkey and humans with wide interspecies variability in the rates of metabolism with monkey and rat exhibiting highest and lowest rates of metabolism, respectively. In all cases the major metabolite formed was an *N*-desmethyl derivative of ABT-773 (M-1). ABT-773 is rapidly cleared in rats after intravenous and oral administration and in dogs by oral administration. For both species, excretion is primarily by the liver with only a small fraction of the dose eliminated in the urine.

The *in vitro* studies across five species including man, suggest that ABT-773 shows a drug-concentration dependent decrease in protein binding. In man, for plasma concentrations above 3 mg/mL, plasma protein binding decreases with increasing total drug concentrations, presumably due to the saturation of the plasma binding sites. Because plasma concentrations of ABT-773 in humans are unlikely to exceed 2 mg/mL at clinically-relevant doses, the concentration dependence is not clinically important. In human plasma, [ $^{14}\text{C}$ ] ABT-773 has a greater affinity for  $\alpha_1$ -acid glycoprotein (AAG) than for human serum albumin (HSA), and plasma protein binding at concentrations of 0.1 to 3  $\mu\text{g/mL}$  was 95.5-95.6%.

ABT-773 is metabolized by human liver microsomes via CYP3A4. The drug also appears to be an inhibitor of CYP3A4 metabolism *in vitro*. The  $IC_{50}$  values obtained for the inhibition of CYP3A4-dependent metabolisms were in the same range as the total steady state peak plasma concentrations of ABT-773 (0.45 - 1.92  $\mu\text{g/mL}$ ) after 200-500 mg BID doses in humans. This indicates the potential for ABT-773 to inhibit the *in vivo* metabolism of coadministered drugs metabolized via CYP3A4.

#### **I.4 Animal Safety Pharmacology**

The pharmacology studies showed that ABT-773 has mild sedative actions with only modest, if any effects on other CNS, CV and/or GI functions at therapeutic to super therapeutic doses/plasma concentrations. These results indicate a minimal risk for marked adverse effects of this compound in clinical studies.

In *in vitro* cellular electrophysiologic studies, supratherapeutic concentrations of ABT-773 (at concentrations 10- and 100-fold above anticipated clinical therapeutic plasma levels) prolong the action potential duration of canine cardiac Purkinje fibers superfused with physiologic salt solutions. These *in vitro* studies likely overestimate the electrophysiologic effects of ABT-773 *in vivo* due to the extensive plasma protein binding of ABT-773. Prolongation of the Purkinje fiber action potential duration *in vitro* is dramatically reduced in the presence of plasma proteins; in the presence of 50% plasma, the dose-response curve for prolongation is shifted rightward, with significant prolongation observed only at 100-fold above the anticipated plasma levels of ABT-773.

When studied in the absence of plasma, the extent of action potential prolongation with ABT-773 is comparable to erythromycin, clarithromycin, and levofloxacin, and less than that of moxifloxacin when compared on the basis of plasma concentration multiples. Studies of M-1, the principal metabolite of ABT-773, demonstrate minimal effects on repolarization and only at high metabolite concentrations (100-fold excess of those found at clinically efficacious concentrations). An *in vivo* toxicology study with non-human primates reveals no significant prolongation of the QTc interval despite long-term exposure to supratherapeutic plasma levels of ABT-773.

#### **I.5 Microbiology**

In the past year, various external investigators have confirmed and expanded the early pre-clinical studies done at Abbott. The activity of ABT-773 against current respiratory tract

isolates including *S. pneumoniae* (macrolide susceptible and resistant), *H. influenzae* and *M. catarrhalis* was examined. An antibiotic surveillance study done by the University of Iowa found the MIC<sub>90</sub> of ABT-773 for *S. pneumoniae* (n=1601) was 0.03 µg/ml. Furthermore, the MIC<sub>90</sub> against low and high level macrolide resistant strains was 0.12 µg/ml. The highest ABT-773 MIC found in the study was 0.5 µg/ml (n=3). The activity of ABT-773 was found to be equivalent to azithromycin and superior to clarithromycin against *H. influenzae* and the ketolide was extremely potent against *M. catarrhalis*. Additional studies done by several other investigators confirmed these findings for respiratory pathogens. Kill kinetic studies with fastidious respiratory pathogens confirmed the bactericidal activity of ABT-773. The ketolide also showed extended post antibiotic effect compared to other macrolides for *S. pneumoniae* and *H. influenzae*.

Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes. Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.

ABT-773 demonstrates *in vivo* efficacy equal or superior to available clinical therapeutics in animal studies against the most prevalent respiratory pathogens including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Once daily (QD) therapy was as effective as twice daily (BID) therapy in treatment of rat pulmonary infections caused by *H. influenzae* and *S. pneumoniae*. ABT-773 also demonstrated efficacy against macrolide and penicillin resistant strains of *Streptococcus pneumoniae*. Efficacy was demonstrated against infections of salient anatomical locations including systemic (septic), inner ear (bullae), pulmonary, and skin abscess suggesting that ABT-773 penetrates into pulmonary tissue and intracellular locations while maintaining activity.



# PART 2

## **Addenda**

- 1.0 Target Product Label**
- 2.0 Clinical Trial Program**
  - 2.1 Clinical Trials (Gantt Chart)**
- 3.0 Chemistry, Manufacturing and Controls**
  - 3.1 Milestones SPD/PPD Chemical Sciences Milestones (Gantt Chart)**
  - 3.2 PARC Milestones (Gantt Chart)**
- 4.0 Non-Clinical**
  - 4.1 Animal Toxicology and Metabolism Milestones (Gantt Chart)**
- 5.0 Project History**
  - 5.1 Expert Strategic Review Process - Summaries**
  - 5.2 Milestones**
  - 5.3 Highlights re: NCE**
  - 5.4 Historical Changes to ABT-XXX Target Product Profile**

## Appendix 1

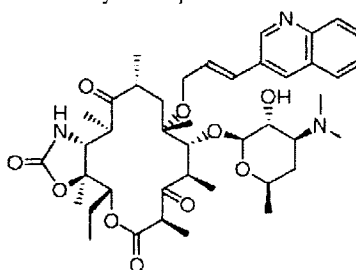
## Target Product Label

**ERADICATE<sup>®</sup> Filmtab<sup>®</sup>**

(eradomycin tablets)

**DESCRIPTION**

Eradomycin is a semi-synthetic ketolide antibiotic. Chemically, it is 11-amino-11-deoxy-3-oxo-5-*O*-desosaminyl-6-*O*-[3'-(3''-quinolinyl)-2'-propenyl] erythronolide<sup>1</sup>. A 11,12-cyclic carbamate. The molecular formula is C<sub>47</sub>H<sub>59</sub>N<sub>3</sub>O<sub>16</sub>, and the molecular weight is 765.94<sup>2</sup>. The structural formula is:



ERADOMYCIN is a white to off-white crystalline powder. It is soluble in acetone, slightly soluble in methanol,

ethanol, and acetonitrile, and practically insoluble in water<sup>3</sup>.

ERADOMYCIN is available as immediate release tablets.

Each ovaloid film-coated ABT-773 tablet contains 150 mg of ABT-773 and the following inactive ingredients:

Cellulose, Microcrystalline, NF

Croscarmellose, Sodium, NF

Hydroxypropyl Cellulose NF

Magnesium Stearate, NF, Impalpable Powder

Silicon Dioxide, Colloidal, NF

Sodium Starch Glycolate, NF Powder

Starch, Pregelatinized, NF

**Plus- coating solution (STILL BEING DEFINED):**

iron oxides, hydroxypropyl methylcellulose, Polyethylene Glycol, Titanium Dioxide, sorbic acid?<sup>4</sup>.

<u>Study #</u>	<u>Comment</u>	<u>Start</u>	<u>End</u>	<u>Investigator/Contact</u>
<sup>1</sup> NA	Confirm chemical name (IUPAC)			Z. Ma
<sup>2</sup> NA	Confirm			Z. Ma
<sup>3</sup> NA	Confirm			Z. Ma
<sup>4</sup> NA	Info correct, how specific is required?			R. Schilling

**CLINICAL PHARMACOLOGY**

ERADOMYCIN is rapidly absorbed from the gastrointestinal tract after oral administration<sup>2</sup>. The absolute bioavailability of 150-mg ERADOMYCIN tablets was approximately 77%<sup>6, 7, 8</sup>. Food effects neither the rate nor extent of ERADOMYCIN absorption. Therefore, ERADOMYCIN tablets may be given without regard to food<sup>9</sup>.

In fasting healthy human subjects, peak serum concentrations were attained within 3 hours after oral dosing<sup>6-11</sup>. Steady-state peak serum ERADOMYCIN concentrations were attained in 3 to 4 days<sup>12</sup> and were approximately 1 µg/ml<sup>1,3</sup> with a 150-mg dose administered every 24 hours. The pharmacokinetics of ERADOMYCIN are non-linear around the recommended dose of 150 mg administered once daily<sup>14-15</sup>. Typical pharmacokinetic parameters of ERADOMYCIN are shown in the following table.

Error! Bookmark not defined.PHARMACOKINETIC PARAMETERS (after 150 mg q 24 h)				
$T_{max}$ <sup>16</sup> (h)	$T_{1/2}$ <sup>17</sup> (h)	$C_{max}$ <sup>18</sup> (ng/ml)	$C_{min}$ <sup>19</sup> (ng/ml)	$AUC$ <sup>20</sup> (ng·h/ml)
2.7 ± 0.6		855 ± 366	29 ± 13	5934 ± 2623

After a 150-mg tablet every 24 hours, approximately 7%<sup>21</sup> of the dose is excreted in the urine as ERADOMYCIN. [No metabolite info presented; may have to defend]. [Does CYP3A have to be mentioned?]. The elimination half-life of ERADOMYCIN was about 6 to 8 hours<sup>22</sup> with 150 mg administered every 24 hours.

The steady-state concentrations of ERADOMYCIN in subjects with impaired hepatic function did not differ from those in normal subjects<sup>23</sup>; the steady-state concentrations of ERADOMYCIN in subjects with impaired renal function did not differ from those in normal subjects<sup>24</sup>. [Will conduct study in elderly<sup>25</sup>; will add comments about

- <sup>5</sup> ~~M00-AAA~~ Definitive biostudy  
<sup>6</sup> ~~M00-BBB~~ Single ascending IV, final, multiple rising dose + p.o.; assumes  
p.o. does not have to be final scale for 800 start  
<sup>7</sup> ~~M00-CCC~~  
<sup>8</sup> ~~M00-DDD~~  
<sup>9</sup> ~~M00-AAA~~ To be part of definitive biostudy  
<sup>10</sup> ~~M97-716~~ 3 hrs based on 716  
<sup>11</sup> ~~M00-AAA~~ Confirmed with definitive biostudy  
<sup>12</sup> ~~M00-024~~ 3-4 days based on 024 study; repeat only if diff. between  
024 and 10-75L scaleup (~~M00-120~~)  
<sup>13</sup> ~~M00-024~~ 024 showed 1 µg/ml; repeat only if diff. between  
024 and 10-75L scaleup (~~M99-129~~)  
<sup>14</sup> ~~M99-018~~ Quantify non-linearity from study  
<sup>15</sup> ~~M00-CCC~~ 150/300/600 mg single comparative study  
If done, 018 would not be used; could also use M99-119 Caucasian section  
<sup>16</sup> ~~M00-018~~ Placeholder study; replace with M00-AAA  
<sup>17</sup> ~~M99-018~~ Placeholder study; replace with M00-AAA  
<sup>18</sup> ~~M99-018~~ Placeholder study; replace with M00-AAA  
<sup>19</sup> ~~M99-018~~ Placeholder study; replace with M00-AAA  
<sup>20</sup> ~~M99-018~~ Placeholder study; replace with M00-AAA  
<sup>21</sup> ~~M00-DDD~~ C14 study, if low number (<20%), multiple dose  
will not be required  
<sup>22</sup> ~~M99-024~~ 6-8 hours based on 024 study; will also be based on M00-AAA  
<sup>23</sup> ~~M99-129~~ Protocol finished  
<sup>24</sup> ~~M00-FFF~~ Low urine excretion will not require results of C14;  
<sup>25</sup> ~~M00-AAA~~ Study in elderly; need final dosage form/dose

gender subanalyses but no specific studies]

[Do we need adolescent study/section in label?]

#### Distribution:

ERADOMYCIN distributes readily into body tissues and fluids. Volume of distribution?<sup>26</sup> Rapid distribution of erandomycin into tissues results in higher erandomycin concentrations in most target tissues than in serum (see table below) [will use either tissue and serum values or only ratios, whichever looks more favorable].

#### Error! Bookmark not defined.CONCENTRATION

(after 150 mg q 24 h)

Tissue Type	Tissue ( $\mu\text{g/g}$ )	Serum ( $\mu\text{g/mL}$ )	T:S Ratio ( $\mu\text{g/mL}$ )
Tonsil <sup>27</sup>	X.X	X.X	X.X
Lung <sup>28, 29</sup>	X.X	X.X	X.X
Epithelial Lining Fluid <sup>30, 31</sup>	X.X	X.X	X.X
Alveolar Macrophage <sup>32, 33</sup>	X.X	X.X	X.X
White Blood Cells <sup>34</sup>	X.X	X.X	X.X
Sinus Mucosa <sup>35</sup>	X.X	X.X	X.X
Cerebral Spinal Fluid <sup>36</sup>	X.X	X.X	X.X
Bronchial Mucosa <sup>37</sup>	X.X	X.X	X.X
Sputum <sup>38</sup>	X.X	X.X	X.X

<sup>26</sup> M-9-000

Absolute bioavailability study

<sup>27</sup> M-9-142

Clinic study; all raw data must be sent to Abbott, will forward to FDA (1/20/99)

<sup>28</sup> M-9-142

<sup>29</sup> M-9-007

Gottfried to executor; contact Gottfried for proposal

<sup>30</sup> M-9-142

Clinic study

<sup>31</sup> M-9-007

<sup>32</sup> M-9-142

Clinic study

<sup>33</sup> M-9-142

<sup>34</sup> M-9-105

Samples being reassayed, orig. results relatively low

<sup>35</sup> M-9-142

TBD; not sure if pursuing

<sup>36</sup> M-9-142

Clinic study

<sup>37</sup> M-9-142

TBD; not sure if pursuing

<sup>38</sup> M-9-142

TBD; not sure if pursuing, ELP is better fluid

## Microbiology:

ERADOMYCIN is a ketolide with concentration-dependent, bactericidal *in-vitro* activity against a wide range of aerobic and anaerobic gram-negative, gram-positive, and atypical microorganisms. ERADOMYCIN exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of bacterial protein synthesis<sup>39 40 41 42</sup>. **ABT-773 binds to the ribosome rapidly, completely, and irreversibly<sup>43</sup>. It appears that these ribosome-binding properties contribute to enhanced activity and lower selection of resistant mutants of gram-positive bacteria relative to other agents that act via the ribosome<sup>44 45 46 47</sup>.** Eradomycin exhibits an in-vitro post-antibiotic effect (PAE), defined as the ability of an agent to sustain antimicrobial action after drug concentrations have fallen below the MIC.<sup>48 49 50</sup>

The mechanism of action of ketolides including eradomycin is different from that of penicillins, cephalosporins, quinolones, aminoglycosides, and tetracyclines<sup>51</sup>. Therefore, **ERADOMYCIN may be active against pathogens that are resistant to these antibiotics<sup>52 53 54 55</sup>. There is no cross-resistance between ERADOMYCIN and the mentioned classes of antibiotics<sup>56</sup>.**

Macrolide resistance occurs principally by two main mechanisms of resistance. Production of ribosomal methylases, either inducible or constitutive, alters the ribosomal target inhibiting macrolide binding; an efflux mechanism pumps the antibiotic from within the microorganism. ERADOMYCIN has been shown in streptococcus to bind to methylated ribosomes<sup>57 58</sup>, to not induce methylase resistance<sup>59 60</sup>, and to bypass the efflux pump<sup>61 62</sup>. **Thus ERADOMYCIN is active against macrolide resistant streptococci<sup>63 64 65</sup>.**

**Resistance to ERADOMYCIN in vitro develops slowly<sup>66</sup>. Resistance to ERADOMYCIN in vitro occurs at a**

<sup>39</sup> <u>990311</u>	Capobianco
<sup>40</sup> <u>990317</u>	Zhang
<sup>41</sup> <u>990332</u>	Zhang
<sup>42</sup> <u>990377</u>	Zhang
<sup>43</sup> <u>990409</u>	
<sup>44</sup> <u>990408</u>	Lichowicz study (serial dilution)
<sup>45</sup> <u>990779</u>	Nofus, will be at ICAAC00
<sup>46</sup> <u>990772</u>	Pendland
<sup>47</sup> <u>990748</u>	
<sup>48</sup> <u>990701</u>	Appelbenun; partial ICAAC99, ICAAC00
<sup>49</sup> <u>990778</u>	Ramirez
<sup>50</sup> <u>990714</u>	Dubois
<sup>51</sup>	Scientifically accepted; provide literature references
<sup>52</sup> <u>990707</u>	
<sup>53</sup> <u>990339</u>	
<sup>54</sup> <u>990558</u>	
<sup>55</sup> <u>990412</u>	
<sup>56</sup>	99051, 99030, 99038, 99042
<sup>57</sup> <u>990209</u>	Zhang mechanism of action reference
<sup>58</sup> <u>990771</u>	Mankin
<sup>59</sup> <u>990419</u>	
<sup>60</sup> <u>990558</u>	Sheenridge
<sup>61</sup> <u>990549</u>	
<sup>62</sup> <u>990338</u>	
<sup>63</sup> <u>990558</u>	Multiple in-vitro studies
<sup>64</sup> <u>990551</u>	
<sup>65</sup> <u>990339</u>	
<sup>66</sup>	<u>99058, 99043, 99079</u>

general frequency of between  $1 \times 10^{-4}$  to  $10^{-6}$ .

ERADOMYCIN has been shown to be active against most strains of the following microorganisms both *in-vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

**Aerobic Gram-Positive Microorganisms**

*Staphylococcus aureus* (methicillin-susceptible strains; macrolide inducibly resistant and efflux strains)

*Staphylococcus epidermidis* (methicillin-susceptible strains)

*Streptococcus pneumoniae* (including penicillin-susceptible, intermediate and resistant strains; macrolide susceptible, intermediate and resistant strains; quinolone susceptible, intermediate and resistant strains)

*Streptococcus pyogenes* including macrolide susceptible, intermediate and resistant strains;

**Aerobic Gram-Negative Microorganisms**

*Haemophilus influenzae* (including beta lactamase producing strains and beta lactamase negative ampicillin resistant (BLNAR) strains)

*Haemophilus parainfluenzae* (including beta-lactamase producing strains)

*Moraxella catarrhalis* (including beta-lactamase producing strains)

**Other Microorganisms**

*Mycoplasma pneumoniae*

*Chlamydia pneumoniae* (TWAR)

*Legionella pneumophila*

The following *in vitro* data are available, but their clinical significance is unknown.

Eradomycin exhibits *in-vitro* minimum inhibitory concentrations (MICs) of  $\leq 2$   $\mu\text{g/ml}$  against most ( $\geq 90\%$ ) strains of the following bacteria; however, the safety and effectiveness of eradomycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

**Aerobic Gram-positive Microorganisms**

*Streptococcus agalactiae*

Streptococci (Groups C, F, G)

Coagulase negative staphylococci (methicillin susceptible)

Viridans group streptococci

***Corynebacterium jeikeium***

*Corynebacterium* spp.

***Listeria monocytogenes***

## Aerobic Gram-negative Microorganisms

### **Bordetella pertussis**

*Legionella pneumophila*

*Neisseria meningitidis*

*Neisseria gonorrhoeae* (including penicillin resistant and quinolone resistant strains)

### Anaerobic Gram-positive Microorganisms

### **Peptostreptococci**

*Propionibacterium acnes*

*Clostridium difficile*

*Clostridium perfringens*

### Anaerobic Gram-negative Microorganisms

*Bacteriodes spp.*

*Porphyromonas spp.*

*Prevotella spp.*

### Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erandomycin powder. The MIC values obtained should be interpreted according to the following criteria:

#### For testing non-fastidious aerobic organisms

MIC (µg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
>8.0	Resistant (R)

#### For testing Haemophilus spp.<sup>a</sup>

MIC (µg/mL)	Interpretation
≤4.0	Susceptible (S)
8.0	Intermediate (I)
≥16.0	Resistant (R)

<sup>a</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (HTM).<sup>2</sup>

#### For testing Streptococcus spp. including Streptococcus pneumoniae<sup>b</sup>

MIC (mcg/mL)	Interpretation
--------------	----------------



≤0.5	Susceptible (S)
1.0	Intermediate (I)
≥2.0	Resistant (R)

<sup>b</sup> These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.<sup>1</sup>

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control bacterial strains to control the technical aspects of the laboratory procedures. Standard eradomycin powder should provide the following MICs with these quality control strains:

Microorganisms	MIC Ranges <sup>68</sup> (µg/mL):
<i>Staphylococcus aureus</i> ATCC 29213	0.016-0.12
<i>Haemophilus influenzae</i> <sup>c</sup> ATCC 49247	1.0-4.0
<i>Streptococcus pneumoniae</i> <sup>d</sup> ATCC 49619	0.002-0.016

<sup>c</sup> This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using ITIM.<sup>1</sup>

<sup>d</sup> This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.<sup>1</sup>

#### Diffusion Techniques

Quantitative methods that require measurement of zone diameters of growth inhibition provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with eradomycin (equivalent to 15-mcg eradomycin) to test the susceptibility of bacteria to eradomycin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a eradomycin disk (equivalent to 15-mcg eradomycin) should be interpreted according to the following criteria.

For testing non-fastidious aerobic bacteria:

Zone Diameter (mm)	Interpretation
>23	Susceptible (S)
20-22	Intermediate (I)
≤19	Resistant (R)

For testing *Haemophilus spp.*<sup>3</sup>:

Zone Diameter (mm)	Interpretation <sup>1</sup>
--------------------	-----------------------------

<sup>68</sup> 2004:1

NCCLS will also have impact

≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant (R)

<sup>c</sup> This zone diameter standard is applicable only to tests with *Haemophilus spp.* using HTM.<sup>2</sup>

For testing *Streptococcus spp.* including *Streptococcus pneumoniae* <sup>4</sup>:

Zone Diameter (mm)	Interpretation <sup>f</sup>
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

<sup>4</sup> These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.<sup>2</sup>

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product)

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the eradomycin equivalent to a 15-mcg eradomycin disk should provide the following zone diameters in these laboratory quality control strains:

#### Zone Diameter Ranges

*Staphylococcus aureus* ATCC 25923 XXXXXmm

*Haemophilus influenzae*<sup>b</sup> ATCC 49247 XXXXXmm

*Streptococcus pneumoniae*<sup>c</sup> ATCC 49619 XXXXXmm

<sup>b</sup> This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM.<sup>2</sup>

<sup>4</sup> This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.<sup>2</sup>

Summaries of susceptibility interpretive criteria and acceptable quality control ranges for eradomycin to be used for validation of susceptibility test results can be shown in the following tables:

#### Susceptibility Interpretive Criteria for Eradomycin

Microorganisms	MIC (μg/mL)			Disk Diffusion (mm)		
	S	I	R	S	I	R
Aerobic Non-Fastidious	<2	4	≥8	≥23	20-22	<19
<i>Haemophilus spp.</i>	<4	8	≥16	≥16	13-15	≤12
<i>Streptococcus spp.</i> including <i>S. pneumoniae</i>	≤0.5	1	≥2	≥20	17-19	≤16

S = susceptible, I = intermediate, R = resistant

Acceptable Quality Control Ranges for Eradomycin To Be Used In Validation of Susceptibility Test Results

Quality Control Strain	MIC (mcg/ml.)	Disk Diffusion (mm)
<i>Streptococcus pneumoniae</i> ATCC 49619	0.002-0.016	XXXXX
<i>Haemophilus influenzae</i> ATCC 49247	0.03-0.12	XXXXXX
<i>Staphylococcus aureus</i> ATCC 25913	0.016-0.12	Not Applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	XXXXX

#### INDICATIONS AND USAGE

ERADOMYCIN FilmTab tablets are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

##### Adults:

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes* (The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. ERADOMYCIN is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of ERADOMYCIN in the subsequent prevention of rheumatic fever are not available at present.)

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae* or *Streptococcus pneumoniae*

Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Chlamydia pneumoniae* (TWAR)

In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended. (For information on development of resistance see **Microbiology** section.)

#### CONTRAINDICATIONS

ERADOMYCIN is contraindicated for patients with a known hypersensitivity to ERADOMYCIN or any macrolide or ketolide antibiotics.

#### WARNINGS

ERADOMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF <sup>69, 70, 71</sup>. (See PRECAUTIONS - *Pregnancy*.)

**Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ERADOMYCIN, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.**

---

69  
70  
71

Seg.  
Seg. 2  
Seg. 3

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

## PRECAUTIONS

### General:

ERADOMYCIN is principally excreted via the liver. ERADOMYCIN may be administered without dosage adjustment to patients with hepatic impairment<sup>72</sup> and normal renal function<sup>73</sup>. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

*Information to Patients:* ERADOMYCIN tablets can be taken with or without food<sup>74</sup>.

### Drug Interactions:

To be written pending outcome of drug interaction studies.

### Planned drug interaction studies:

- 1) Ketoconazole<sup>75</sup>
- 2) Impact of rifampin on 773<sup>76</sup>
- 3) Impact of 773 on oral contraceptives<sup>77</sup>
- 4) Impact of 773 on theophylline<sup>78</sup>
- 5) Digoxin<sup>79</sup>
- 6) Impact of 773 on midazolam<sup>80</sup>
- 7) Nifedipine<sup>81</sup>
- 8) Statin<sup>82</sup>
- 9) Warfarin<sup>83</sup>
- 10) Carbamazepine<sup>84</sup>
- 11) Cyclosporin<sup>85</sup>
- 12) Loratadine<sup>86</sup>

Potentially add general CYP3A statements rather than individually doing studies on individual drugs

### Mutagenesis, Carcinogenesis, Impairment of Fertility:

<sup>72</sup> <u>M99-126</u>	Hepatic study
<sup>73</sup> <u>M00-155</u>	Renal study
<sup>74</sup> <u>M00-156</u>	Fertil bio study
<sup>75</sup> <u>100099</u>	
<sup>76</sup> <u>100099</u>	M00-156
<sup>77</sup> <u>100100</u>	M99-128
<sup>78</sup> <u>100101</u>	M99-139
<sup>79</sup> <u>100102</u>	
<sup>80</sup> <u>100089</u>	M00-155: If does not increase midazolam conc (not likely), no need to do 100103 or 100104
<sup>81</sup> <u>100103</u>	Pending
<sup>82</sup> <u>100104</u>	Pending
<sup>83</sup> <u>100105</u>	
<sup>84</sup> <u>100107</u>	
<sup>85</sup> <u>100108</u>	
<sup>86</sup> <u>100109</u>	

The following *in vitro* mutagenicity tests have been conducted with ERADOMYCIN:

In Vitro Cytogenetics Assay in Human Lymphocytes<sup>87</sup>  
 Mouse Lymphoma Assay<sup>88</sup>  
 Mouse Micronucleus Test<sup>89</sup>  
 Bacterial Reverse-Mutation Test (Ames Test)<sup>90</sup>

All tests had negative results.

Fertility and reproductive studies have shown that daily doses of up to ? mg/kg/day (X times the recommended maximum human dose based on mg/m<sup>2</sup>) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after ? mg/kg/day were X times the human serum levels.<sup>91-93</sup>

In rabbits, no treatment-related effects on fetal viability or growth were observed.<sup>94</sup>

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ERADOMYCIN.

**Pregnancy:** Category B or C<sup>95</sup>.

X number teratogenicity studies in rats (three with oral doses and one with intravenous doses up to X mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to X mg/kg/day (approximately X times the recommended maximum human dose based on mg/m<sup>2</sup>) or intravenous doses of X mg/kg/day administered during gestation days X to X failed to demonstrate any teratogenicity from ERADOMYCIN. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of X mg/kg/day administered during gestation days X to X. Plasma levels after X mg/kg/day were X times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of X mg/kg/day (X and X times the recommended maximum human dose based on mg/m<sup>2</sup>, respectively) during gestation days X to X. Cleft palate was also seen at X mg/kg/day. The X mg/kg/day exposure resulted in plasma levels X times the human serum levels. In monkeys, an oral dose X mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m<sup>2</sup>) produced fetal growth retardation at plasma levels that were X times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. ERADOMYCIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

**Nursing Mothers**<sup>96</sup>:

It is not known whether ERADOMYCIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ERADOMYCIN is administered to a nursing woman. It is known that ERADOMYCIN is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

<sup>87</sup> [100111](#)  
<sup>88</sup> [100114](#)  
<sup>89</sup> [100115](#)  
<sup>90</sup> [100117](#)  
<sup>91</sup> [100118](#) Seg 1  
<sup>92</sup> [100120](#) Seg 2 (rats)  
<sup>93</sup> [100119](#) Seg 3  
<sup>94</sup> [100126](#)  
<sup>95</sup> [100119](#) Seg 3  
<sup>96</sup> [100119](#) Study TBD

*Pediatric Use:*

The safety and effectiveness of ERADOMYCIN in pediatric patients have not been established. [If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.]

*Geriatric Use<sup>97</sup>:*

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 150 mg every 24 hours, the maximum serum concentrations and area under the curves of ERADOMYCIN were increased<sup>97</sup> compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

[If clinical studies did not include sufficient numbers (100) of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection of PRECAUTIONS shall include the following statement: "Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."]

**ADVERSE REACTIONS**

The majority of side effects observed in clinical trials were of a mild and transient nature.

The most frequently reported events in adults were diarrhea (X%), nausea (X%), abnormal taste (X%), dyspepsia (X%), abdominal pain/discomfort (X%), and headache (X%)<sup>98</sup>. Most of these events were described as mild or moderate in severity. Of the reported adverse events, only X% was described as severe.

In sinusitis studies conducted in adults comparing ERADOMYCIN to amoxicillin/clavulanic acid, there were fewer adverse events involving the digestive system in ERADOMYCIN-treated patients compared to amox/clav-treated patients (X% vs X%; p<0.01). Twenty percent of amoxicillin/clavulanic acid-treated patients discontinued therapy due to adverse events compared to 4% of ERADOMYCIN-treated patients.

Taste/Gil comparable to Zithromax in AECB study?

*Changes in Laboratory Values<sup>99</sup>:* Changes in laboratory values with possible clinical significance were as follows:

Hepatic - elevated SGPT (ALT) < X%; SGOT (AST) < X%; GGT < X%; alkaline phosphatase < X%; LDH < X%; total bilirubin < X%

Hematologic - decreased WBC < X%; elevated prothrombin time X%

Renal - elevated BUN X%; elevated serum creatinine < X%

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

**DOSAGE AND ADMINISTRATION**

ERADOMYCIN<sup>®</sup> Filmtab<sup>®</sup> (ERADOMYCIN tablets) may be given with or without food<sup>100</sup>.

<sup>97</sup> M97-AAA Study in elderly: need final dosage form/dose  
<sup>98</sup> Phase III studies

<sup>100</sup> 150064 M97-716

**Error! Bookmark not defined. ADULT DOSAGE GUIDELINES**

<b>Infection</b>	<b>Dosage (q24h)</b>	<b>Normal Duration (days)</b>
Pharyngitis/Tonsillitis	150 mg	5 days
Acute bacterial sinusitis	150 mg	10 days
Acute exacerbation of chronic bronchitis:	150 mg	5 days
Community-acquired pneumonia including <i>mycoplasma</i> , <i>chlamydia</i> and <i>legionella</i>	150 mg	7-10 days

ERADOMYCIN may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function<sup>161, 162</sup>.

**HOW SUPPLIED**

ERADOMYCIN<sup>®</sup> Filmtab<sup>®</sup> (ERADOMYCIN tablets) are supplied as COLOR oval film-coated tablets containing 150 mg of ERADOMYCIN imprinted (on one side) in COLOR with the Abbott logo and a two-letter Abbo-Code designation, DK, in the following packaging sizes:

Bottles of 30 (NDC XXXX-XXXX-XX), ABBO-PAC unit dose strip packages of 100 (NDC XXXX-XXXX-XX), and RAD-PAK<sup>™</sup> unit-of-use compliance package of 5 tablets in individual blisters.

**CLINICAL STUDIES****Indication XXX**

In a controlled clinical study of XXX performed in the United States, where significant rates of both penicillin-resistant and macrolide-resistant *Strep. pneumoniae* were observed, ERADOMYCIN was compared to XXX. In this study, very strict evaluability criteria were used to determine clinical response. For the XXX patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was XX% for ERADOMYCIN and XX% for the XXX.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. The following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

<sup>161</sup> ~~100070~~ Hepatic study (M99-126)  
<sup>162</sup> ~~100081~~ Renal study (TBD)

**Error! Bookmark not defined.U.S. Acute XXX Study**  
**ERADOMYCIN vs. Comparator XXX**

<b>EFFICACY RESULTS</b>	
<b>PATHOGEN</b>	<b>OUTCOME</b>
<i>S. pneumoniae</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>H. influenzae</i> *	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>M. catarrhalis</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>S. pyogenes</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
Overall	ERADOMYCIN success rate X/X (X%), control X/X (X%)
None of the <i>Strep. pneumoniae</i> isolated pre-treatment was resistant to ERADOMYCIN; X% were resistant to the control agent.	

**Safety:**

The incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the two agents.

In two other controlled clinical trials of indication XXX performed in the United States, where significant rates of penicillin-resistant and macrolide-resistant *Strep. pneumoniae* were found, ERADOMYCIN was compared to XXX. In these studies, very strict evaluability criteria were used to determine the clinical responses. In the XXX patients who were evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was XX% for both ERADOMYCIN and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

**Error! Bookmark not defined.Two U.S. Acute XXX Studies**  
**ERADOMYCIN vs.**  
**Comparator XXX**

<b>EFFICACY RESULTS</b>	
<b>PATHOGEN</b>	<b>OUTCOME</b>
<i>S. pneumoniae</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>H. influenzae</i> *	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>M. catarrhalis</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
<i>S. pyogenes</i>	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
Overall	ERADOMYCIN success rate, X/X (X%), control X/X (X%)
Of the <i>Strep. pneumoniae</i> isolated pre-treatment, X% were resistant to ERADOMYCIN and X% were resistant to the control agent.	

**Safety:**

The incidence of adverse events in all patients treated, primarily diarrhea (X% vs. X%) and XXX (X vs. X%)



was clinically and statistically lower in the ERADOMYCIN arm versus the control arm.

#### ANIMAL PHARMACOLOGY AND TOXICOLOGY

ERADOMYCIN is rapidly and well-absorbed with dose-linear kinetics, low protein binding, and a high volume of distribution. Plasma half life ranged from 1 to 6 hours and was species dependent. High tissue concentrations were achieved, but negligible accumulation was observed. Fecal clearance predominated. Hepatotoxicity occurred in all species tested (i.e., in rats and monkeys at doses 2 times greater than and in dogs at doses comparable to the maximum human daily dose, based on  $\text{mg}/\text{m}^2$ ). Renal tubular degeneration (calculated on a  $\text{mg}/\text{m}^2$  basis) occurred in rats at doses 2 times, in monkeys at doses 8 times, and in dogs at doses 12 times greater than the maximum human daily dose. Testicular atrophy (on a  $\text{mg}/\text{m}^2$  basis) occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose. Corneal opacity (on a  $\text{mg}/\text{m}^2$  basis) occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose. Lymphoid depletion (on a  $\text{mg}/\text{m}^2$  basis) occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose. These adverse events were absent during clinical trials.

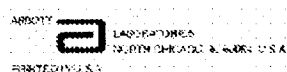
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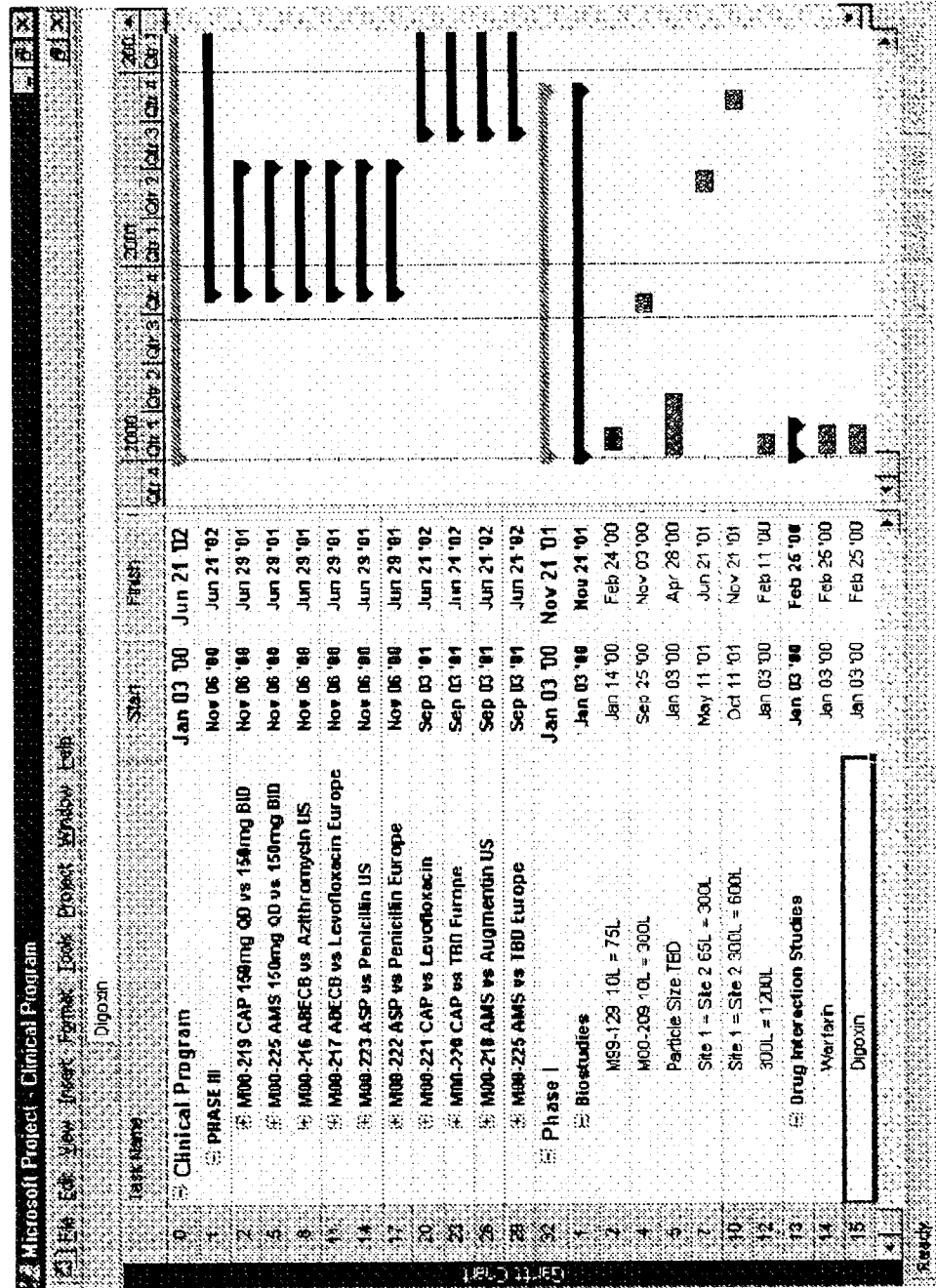
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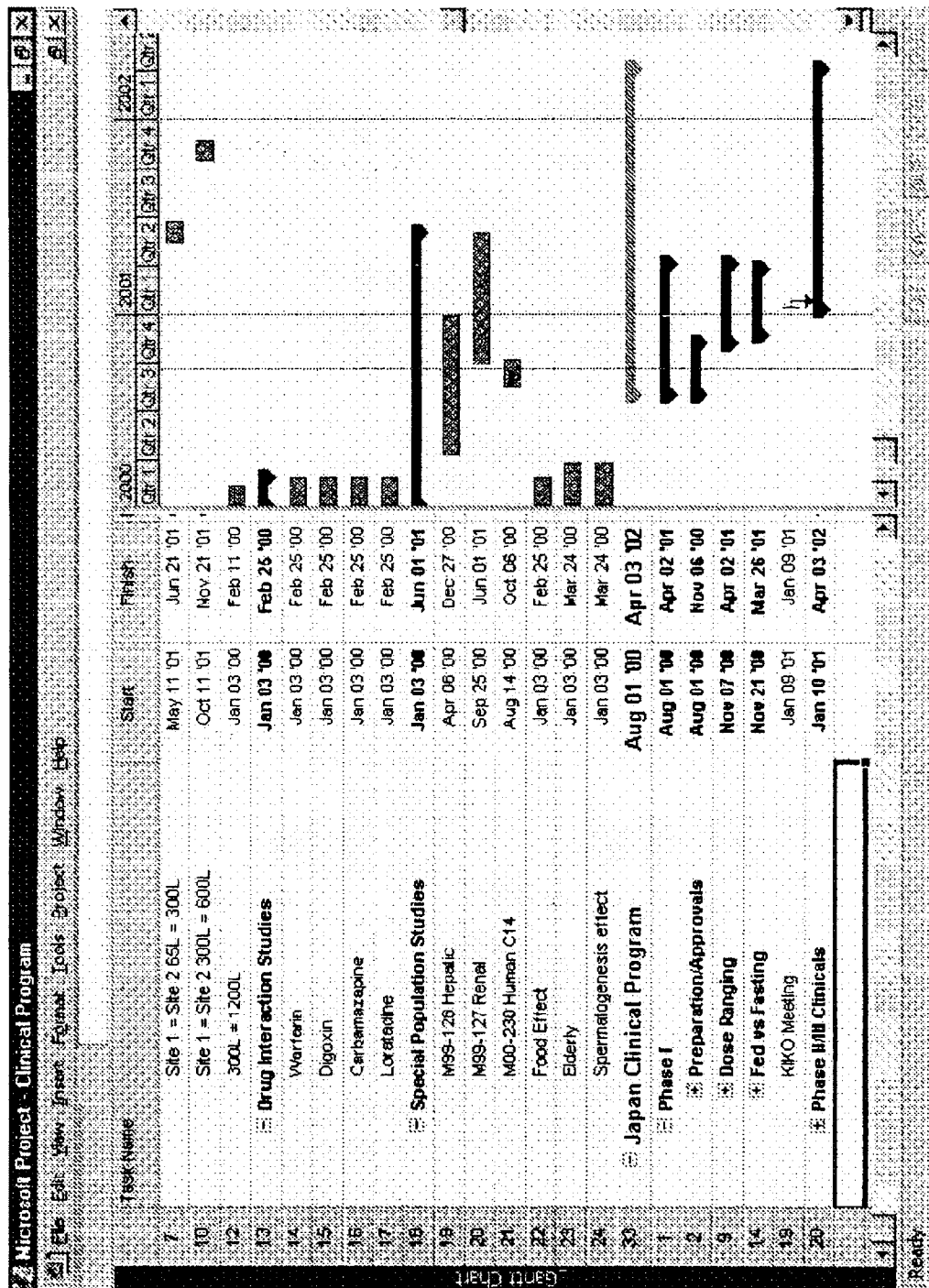
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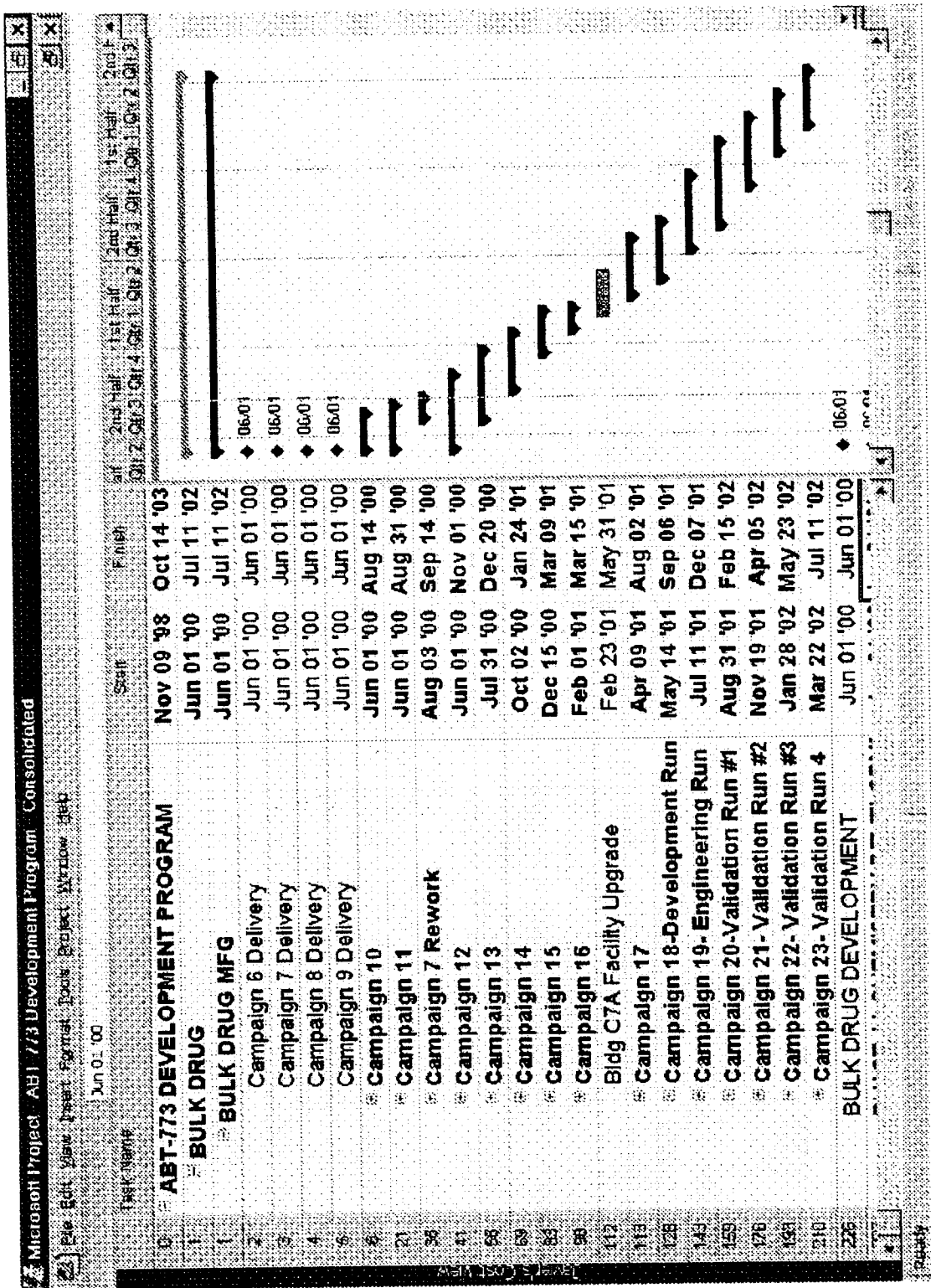
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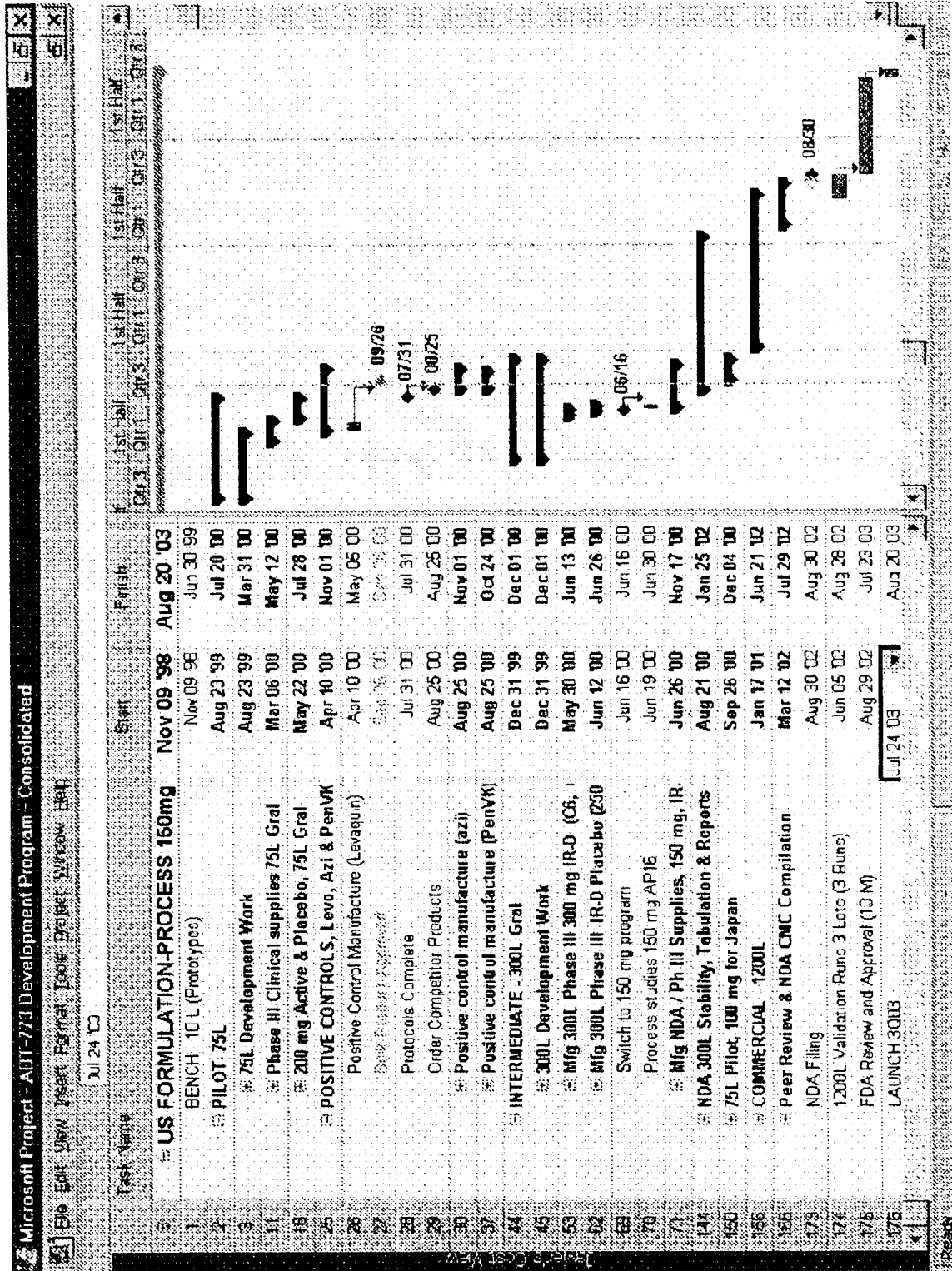
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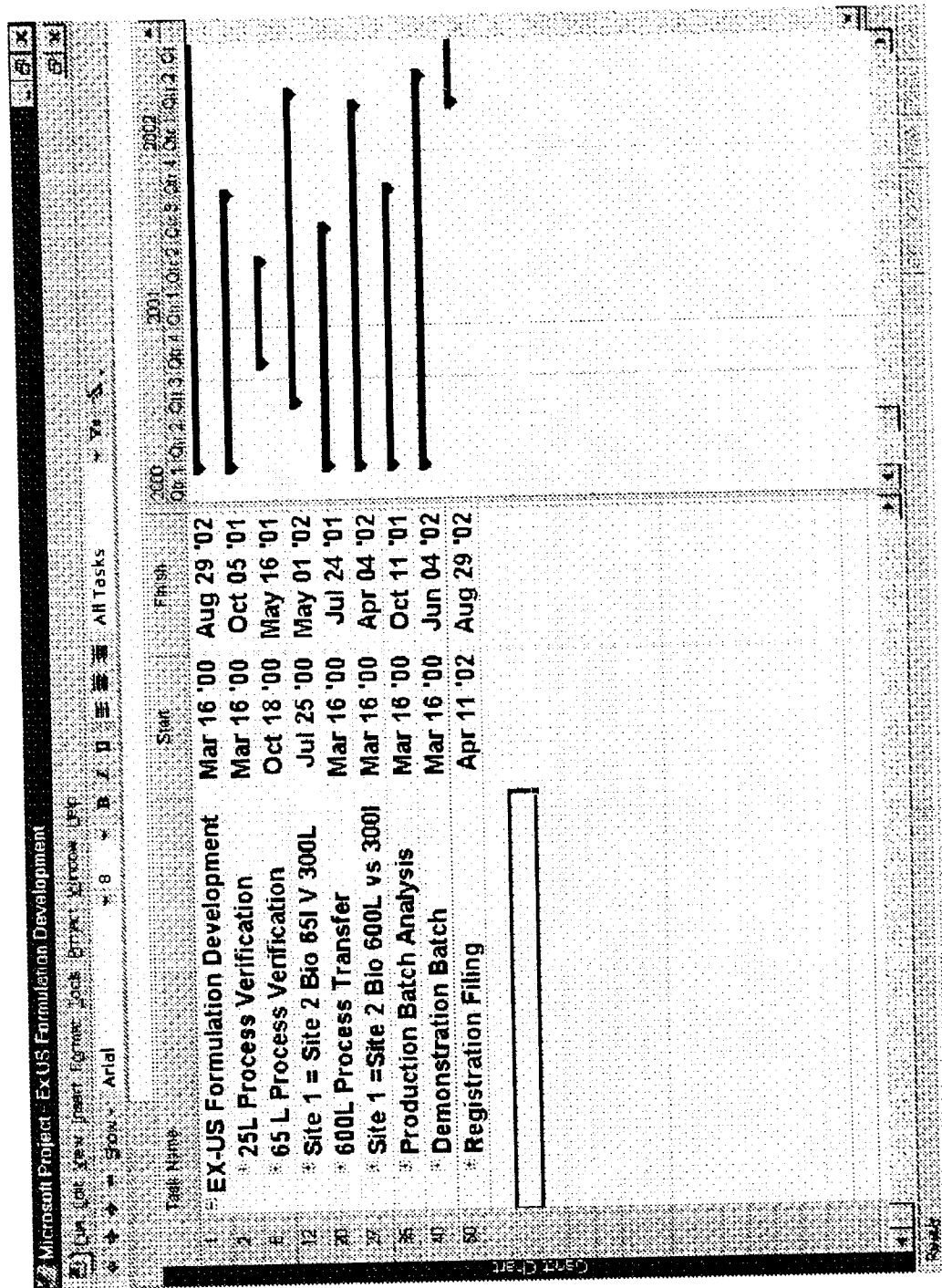
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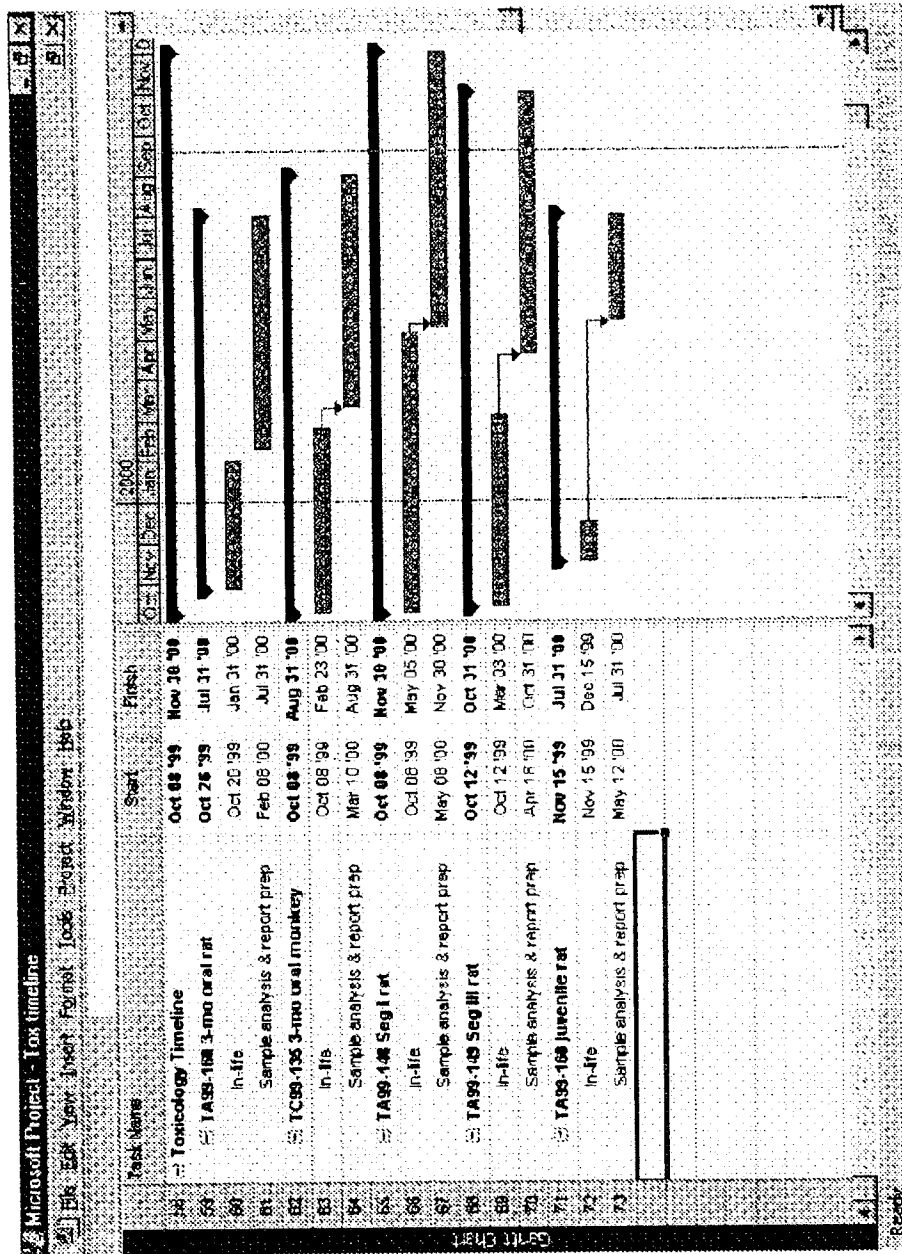
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## 5.0 Project History

### 5.1 Expert Strategic Review Process - Summaries

#### 5.2 Highlights re: NCE

- ABT-773 was approved by PPCC in 03/97 for development by the Macrolide Venture. Projected NDA date was 12/00.
- Fifty kg of drug was delivered in 1997. Drug chemistry and cost of drug was a major challenge to development cost and timing. NDA projected date was moved to 03/01 with 50% probability.
- First Phase I study was initiated in Netherlands in 11/97. Based on PK results, the request for a QD 1R formulation and no major breakthroughs in chemistry, the NDA projected date was moved to 06/02 with 80% probability.
- All process chemistry efforts and delivery activities were put on hold in 0-1/98 due to concerns of GI/taste issues with the drug. A comparative safety study using 300mg and 600mg/day of ABT-773 vs Clari 500mg bid was initiated. NDA projected date was moved to 09/02 with 80% probability.
- The encouraging safety results lifted the hold on the process chemistry and delivery activities. For 5 months there were no efforts on process research and delivery activities for drug substance. The first ER prototypes were not acceptable. A Phase IIA study using unformulated capsules was initiated in Europe in AECB patients by end of 1998. NDA projected date was kept at 09/02 with 80% probability.
- Significant breakthroughs were achieved in bulk drug synthesis and an ambitious development program was initiated by end of 1998 to develop a QD formulation. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen on 8/99 for further development based on pharmacokinetics, safety, and ease of manufacture. The Venture had undertaken a challenging chemistry, formulation and clinical development plan and the NDA projected date had been brought forward to 12/01.
- The Phase 2a study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patient compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen.
- Three Phase 2b studies were started in Sept. 1999 in both the US and EU investigating ABT-773 once daily doses. M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days). M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days). M99-048 - Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)
- Scale-up activities to develop a 300mg tablet were initiated at the 75L pilot scale in 9/99, moving to a 300L intermediate scale in Jan 2000. A bioequivalence study was successful comparing the bench scale clinical lots to the 75L pilot scale lots.



- The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABSCB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.
- The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.
- Based on the Phase 2b efficacy and safety results, the decision was made to change the tablet dose from 300mg to 150mg. This decision moved the regulatory filing date forward 8 months to Aug 2002 and postponed the start date of the Phase III clinical studies to Nov 2000, in order to prepare 150mg clinical supplies.
- A Japanese bridging study was conducted in Hawaii to evaluate safety and pharmacokinetics of Japanese and non-Japanese subjects. Over the studied doses (150, 300 and 600 mg single and multiple QD), ABT-773 AUC but not C<sub>max</sub> deviated from dose-proportionality in the Japanese and non-Japanese subjects. At equivalent doses, the Japanese subjects had about 50% greater ABT-773 AUC than the non-Japanese subjects. Based on this result, the Japanese Phase I program will be repeated in Japan. Once Phase I results are available and the clinical agency KIKO has been consulted, the Phase II/III program in Japan will be finalized. It is unknown at this time if a separate Japanese dose will be required.

### 5.1 Historical Changes to ABT-XXX Target Product Profile

Table 4.0.a Historical Changes to ABT-XXX Target Product Profile		
PPCC/DDC Profile (12/10/97)	Current Profile (9/00)	Rationale for Profile Change
Activity against Gram +, Gram -, atypicals	Activity against Gram +, Gram -, atypicals	No Change
Activity against <i>H. influenzae</i> = az	Activity against <i>H. influenzae</i> = azi	No Change
Active against 80% of Gram + resistant strains of efflux and MLS c	Active against 80% of Gram + resistant strains of efflux and MLS c	No Change
Active against most macrolide resistant pathogens on a bacterial worldwide susceptibility panel	Active against most macrolide resistant pathogens on a bacterial worldwide susceptibility panel	No Change
Maintain balanced plasma/tissue levels similar to clar	Maintain balanced plasma/tissue levels similar to clar	No Change
Incidence of GI side effects=cephalosporins	Incidence of GI side effects=azi	Azithromycin is a more important competitor in the U.S.
Incidence of drug-interactions = clar, no contraindications	Incidence of drug-interactions = clar, no contraindications	No Change
QD dosing adult/tablet	QD dosing adult/tablet	No Change
QD dosing ped OS	QD dosing ped OS	No Change
BID dosing for IV	QD dosing for IV	Current competition is QD
Less painful IV at injection site than clar	Comparable pain at injection site than azi	Azi has less pain than clar.
Less metallic taste for tablet than clar.	Less metallic taste than clar XL	Clar XL now available.

OS equal in taste to cephalosporins	OS equal in taste to Azi/ Omnicef	Azi and Omnicef most important comparators.
5-day therapy for most indications, up to 10 days for serious infections. 3 day therapy for pharyngitis.	5-day therapy for most indications	No Change
Bulk drug cost less than \$2500/kg at launch and \$1250/kg 3 years post launch.	COGS > 80% SMM/ at launch	No Change
Maximum adult dose per day of 1 gram.		No Change
Can be given with or without food.		Food effect study to be repeated with final formulation, current studies indicate better absorption with food.

**ABT-773 Update February 12, 2001****Introduction**

ABT-773 is a ketolide antimicrobial, an evolutionary step from the macrolide antimicrobials such as erythromycin and the new generation macrolides like clarithromycin and azithromycin. It is in phase III development as a replacement to clarithromycin.

The antibiotic market is a large market (\$20.5 Billion in 1999) and is expected to expand on a global sales basis (\$26.5 Billion in 2005). The majority of the markets sales are in the oral tablet/capsule segment. Market sales increases are being driven by replacement of older/cheaper agents with branded agents. Zithromax has driven market demand for cost/convenience/tolerability, while the quinolones (Levaquin, Tequin, Avelox) are the fastest growing segment, playing into resistance concerns. Resistance is a major driving force for both the quinolones and ketolides development.

**Ketolides are a Novel Class of Antimicrobial**

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 is the most active ketolide presently under development. It is 5 to 10 times more active than telithromycin (Aventis ketolide) against *S. pneumoniae* and *S. pyogenes* including resistant strains. It has equal activity to telithromycin and azithromycin against *H. influenzae*. The increased activity can be attributed increased ribosomal binding. Compared to macrolides that bind only to domain V, ABT-773 binds to both domains II and V. The binding is essentially irreversible and provides bactericidal activity against *S. pneumoniae*.

**Key issues facing the ABT-773 development program are summarized below****QTc Issues**

The potential for QTc prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide. Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies. There is considerable scientific uncertainty in relating the findings from in vitro assays and animal models to clinical risk of malignant arrhythmias. In an effort to gain more

knowledge these agencies are requiring the pharmaceutical companies to do additional test including

- ICH guidelines require data from animal models and 200 patients
- FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
- FDA has question whether ketolides behave like macrolides
- FDA requested additional dog tox work to evaluate QTc of ABT-773
- ABT-773 studies required including ECG monitoring in pivotal Phase 3 studies.
- FDA may require a Phase I study in patients with underlying cardiac disease, but the design for these studies has not been determined.
- Some antimicrobials now contain warnings for QT prolongation such as moxifloxacin.
- Telithromycin (Ketek) data residing at FDA will be reviewed by FDA Advisory Committee at a meeting scheduled for May 2001 probably related to concerns about efficacy and not related to QTc concerns.

The ketolide ABT-773 will be considered guilty until proven innocent because it is related to erythromycin and clarithromycin which are also suspect and under scrutiny. ABT-773 has the following data related to its potential or lack of potential to affect the QT interval.

- Preclinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose  $\geq 800$  mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

The Venture plan for dealing with the uncertainties related to developing a drug which has an unknown potential for prolonging the QT intervals is to pro-actively attempt to find out as much about our drug and the science related to QTc by;

- Completed preclinical evaluation of ABT-773
- Initiate FDA recommended dog studies.
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Perform FDA requested study of QTc in patients with pre-existing cardiac disease; perform phase I study as required by CPMP.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.

#### **Liver Toxicity Issues**

The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QTc issues, since both of these problems have resulted in

# PART 3

drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all antimicrobials are under going extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity, scheduled for February 11-12, 2001. Jean Fox will attend this meeting and report back on it so that we will be able to update this topic at the February meeting.

In the Japanese bridging study run in Hawaii we saw increases in LFTs in Japanese subjects. This was very disturbing, since increases in LFTs were seen only in the Japanese subjects. In addition the Japanese subjects had AUCs which were 50% higher than the western subjects. LFTs in over 1000 western subjects did not show any problems. Since, the Japanese subjects with elevated LFTs did not show a dose response, it was felt that the changes in LFTs might be related to the high caloric diet on the unit. To answer this question Phase I food interaction and a repeat of the bridging study was preformed in Japan. The results of this study showed no evidence of any problem with LFTs in the Japanese or Caucasians. Based on the encouraging results we will continue moving forward with the Japan Program.

#### **Phase III Tablet Program**

The Phase III tablet program is underway after several delays related to manufacturing of the 150 mg tablet to replace the 300 mg tablets and the late date (11/27/00) of the FDA End of Phase II meeting. The present plan is to complete the Phase III 150 mg once daily indications in the US and Europe this year. These studies include two pharyngitis studies compared to penicillin 500 mg TID, one ABECB study in the US compared to Azithromycin, and one European ABECB study compared to Levofloxacin. The CAP and sinusitis dose selections studies are running globally, but no European sites are enrolling yet due to the changes in the protocol following the FDA End of Phase II meeting. We are increasing sites and planning to go to the Southern Hemisphere if needed to complete the studies before the start of the fall respiratory season. These changes have added additional costs that will add approximately \$5.0 MM to the budget.

The results of the CAP and Sinusitis studies have the potential of generating divergent development paths based on differences in AI and PPD regulatory and commercial considerations. PPD would prefer to have 150 mg once daily for all indications and AI would prefer 150 mg once daily for pharyngitis and ABECB and 150 mg BID for CAP and sinusitis. Once we complete the study we will need to meet to iron out the possible options.

#### **ABT-773 IV Formulation Program**

The IV formulation program is presently unfunded. The IV program is important to overall program because of the following;

- Hospital formulary acceptance
- XX% share gain in Tab sales due to step-down therapy
- Positions 773 for serious infections
- Support for *S. pneumoniae* resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provide additional information on QTc effects

The ABT-773 IV program received partial funding last year both from PPD and HPD, but has not been funded for 2001. The following outlines the IV program fund and funding needed.

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
  - Formulation development (lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV (\$7MM)
  - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)

The clinical program with 2001 funding decision in February will included;

- |  |         |
|--|---------|
| • Single Dose-rising Phase I study         | Apr/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND                              | Oct/01  |
| • Initiate Phase III                       | Dec/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |

The Venture would recommend funding the Phase I study to determine safety and tolerability profile as a GO/No Go decision. Assuming a GO decision we would need \$7 MM 2001 to start Phase III program.

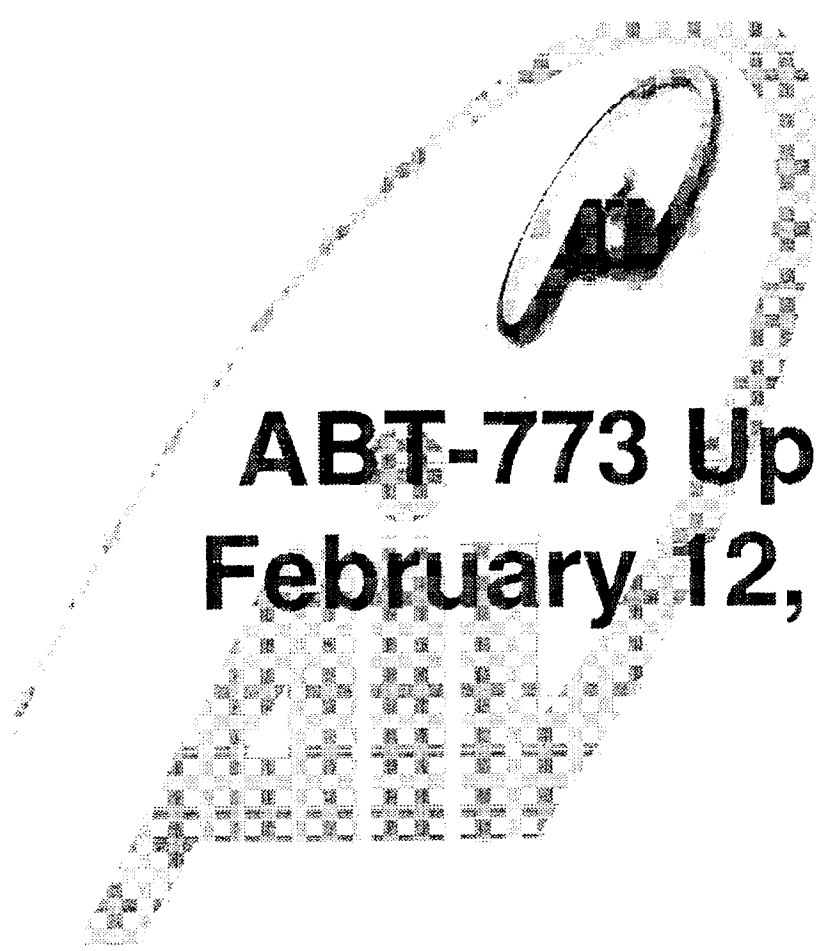
#### **Pediatric Program**

The pediatric suspension program is on hold. ABT-773 is 5 to 7 times more bitter than clarithromycin. This will make the development of an acceptable formulation very difficult. The first prototype tested had a taste that was better than clarithromycin but not as good as azithromycin. The pharmacokinetics showed AUCs that were only 70% of the tablet formulation. Even with the difficulties of making an acceptable formulation the pediatric formulation would have benefits including increasing the perception of safety, better pricing and acceptance in European markets, and FDA requires studies in pediatrics. The Venture would recommend continuing the hold until we resolve other issues and then re-evaluate possible ways of overcoming the taste problem.

#### **Japan Development Program**

The Japan development program is planned in coordination with Taisho and Dainabot. Taisho funds 10.69% of global development costs and 50% of local Japan costs. The Venture is attempting to use a bridging strategy as the primary plan for development in Japan. The Phase I studies in Japan which were initiated in response to the LFT problems in the first bridging study, have been completed. There were not increases in the LFTs of the Japanese or Caucasians in the study. We will be meeting with Taisho and Dainabot to formulate a plan to present to Kiko in the 2<sup>nd</sup> or 3<sup>rd</sup> Quarter.





# **ABT-773 Update February 12, 2001**

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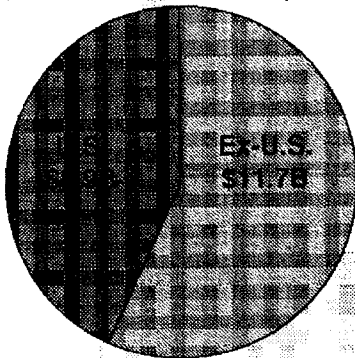
# Agenda

- Introduction
- The molecule
- Phase III tablet program Issues
  - QT
  - Liver Function
  - Dosing
- IV program
- Pediatric program
- Japan program

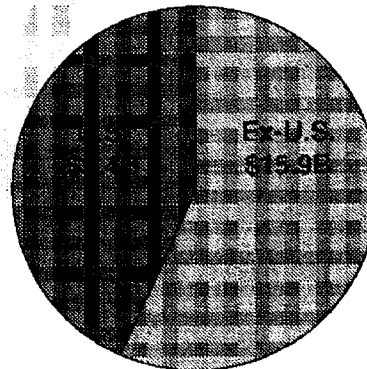


## Global Antibiotic Market Sales Current vs Future Projection

1999 Global Sales \$20.6B



2005 Global Sales \$25.3B



The antibiotic market is a large market and is expected to expand on a global sales basis



## Global Market Drivers

### Negative vs Positive Drivers

- **Antibiotic Resistance**

Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓

Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

- **Patent Expirations**

May increase price sensitivity and bargaining power of MCOs ↓

Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑

- **Market expansion ex-US ↑**

- **Unmet Need ↓**

–Overall unmet need relatively low

–Cost, convenience, tolerability take on added importance

–Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

- **Competition ↓**

–6 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracel, Ketek, Zynox

–Continued discovery/development activity by key competitors

–High level of promotional activity

Negative driver ↓

Positive driver ↑

## Key Success Factors

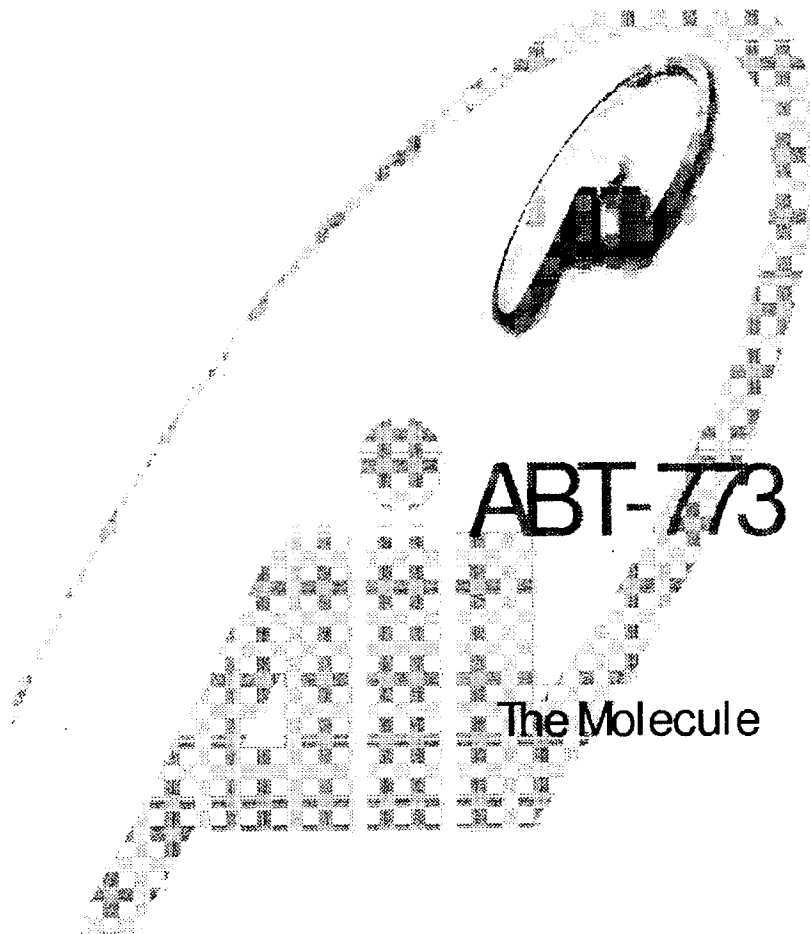
### US vs ex-US

		U.S. Assessment	Ex-U.S. Assessment
Profile	Efficacy	++ Requires a certain baseline level of efficacy across all indications as a "ticket to entry", but is difficult to differentiate agents based on efficacy	+++ While also difficult to differentiate based on efficacy, efficacy takes on added importance with respect to regulatory approval, especially in CAP
	Tolerability	+++ Success of Zithromax and Levaquin have redefined expectations for tolerability of new agents, agents must offer very good tolerability given numerous alternatives	++ Although important, markets are willing to bear somewhat higher incidence of adverse events, provided they are not severe (i.e. taste perversion); over time, however, AE hurdles will continue to be increased
	Convenience	+++ Zithromax and recent quinolones have moved the market toward short course therapies dosed once daily. Biaxin in 1991 represented the last major BID entrant	++ While in some cases durations are even shorter (azithromycin), market imposes relatively minor penalties for BID dosing
	Reputation/Claim	++ Important to leverage the overall ketolide message, and to maximize regulatory access, although availability of data may be able to accomplish same end	+++ May prove critical in the regulatory decision of approvability, as well as in setting premium pricing
	Price	++ Able to set price in accordance with optimal price/demand relationship; only moderate price sensitivity in market, though this could increase with increased number of generic competitors over mid-term	+++ Pricing figures heavily into the overall profitability of the compound and is governed by merits of product profile relative to other agents
Regulatory	Approvability	++ With data showing equivalence to comparators, is not a major area of concern	+++ Will take into consideration PK profile in addition to clinical data, which could weaken argument for approval; given the pivotal nature of CAP approval to overall compound viability, regulatory risk is magnified; will require very strong clinical data if 150 mg OD is to be supported
Profitability	COGS	++ Allows for ~30% SMM given price parity to Zithromax	++ Due to pricing constraints, COGS represents a larger issue; current estimates are 76% SMM at launch rising to 67% peak
	Price	++ Assumes price parity to Zithromax	+++ Profile may limit optimal pricing

+ Minor Factor

++ Moderate Factor

+++ Major Factor



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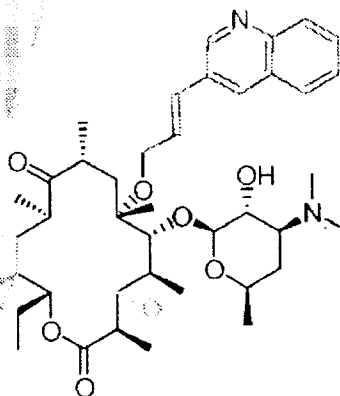


## ABT-773 Ketolide

- Quinolylallyl propenyl moiety at the 6-O-position

- Keto group at the 3-position

- Carbamate group at the 11, 12-position



**ABT-773**



## ABT-773 Ketolide

- **Ketolides are a Novel Class of Antimicrobial**

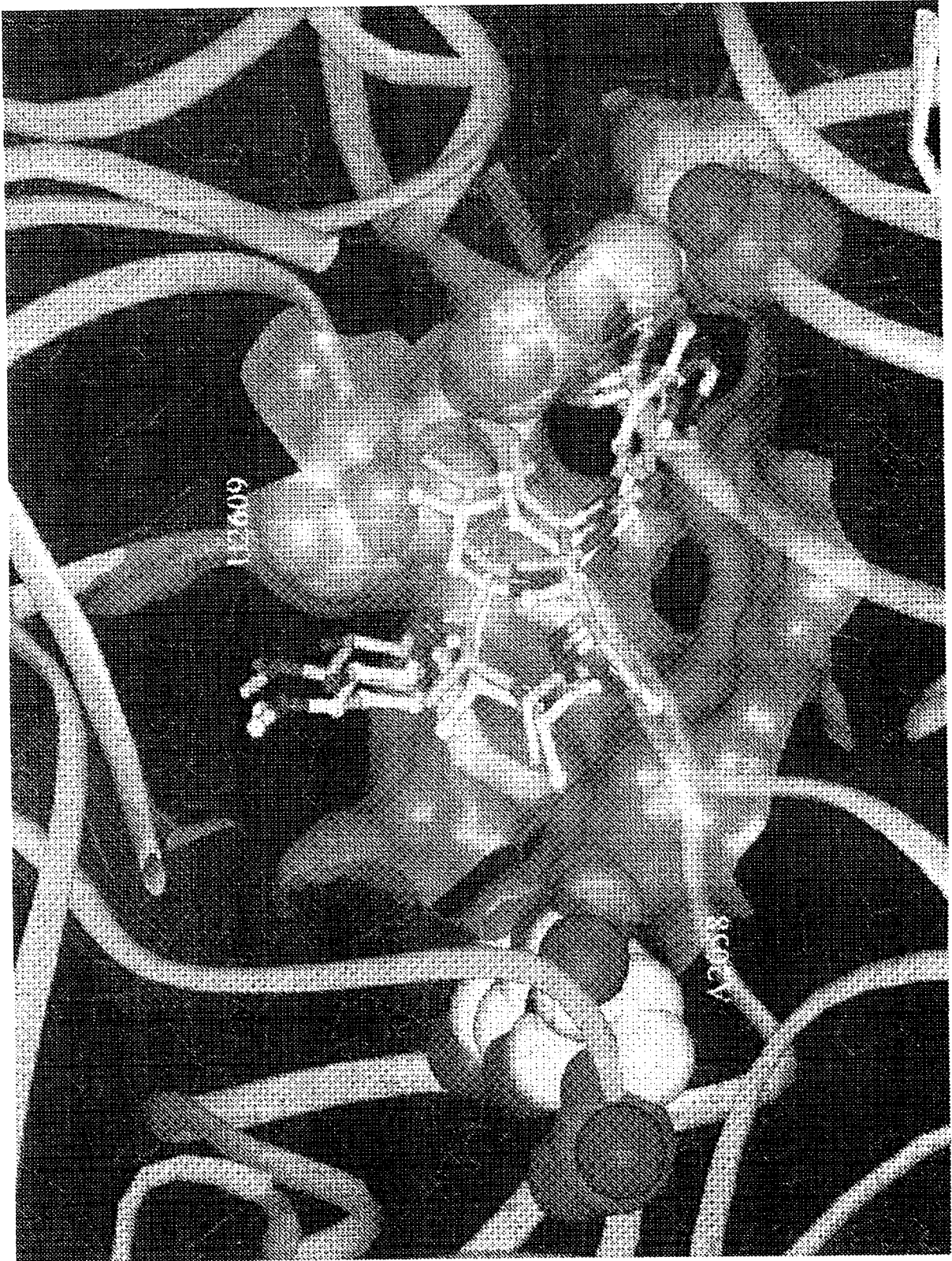
- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development





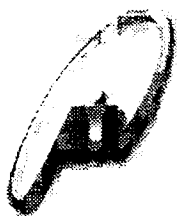
## Microbiology

Organism	MIC <sub>90</sub> $\mu$ g/ml			
	ABT-773	Ketek	Clari	Azi
<i>S. pneumoniae</i> ery-S	0.008	0.004	0.03	0.12
<i>S. pneumoniae</i> mef	0.12	1.0	4.0	16.0
<i>S. pneumoniae</i> erm	0.01	0.12	>32	>32
<i>S. pyogenes</i> ery-S	0.12	2.0	1.0	2.0
<i>S. pyogenes</i> ery-R	0.5	>8.0	>32	>32
<i>M. catarrhalis</i>	0.25	0.25	0.5	0.25
<i>H. Influenzae</i>	2.0	2.0	16	2.0
Legionella	2.0	2.0	0.06	1.0
<i>M. Pneumoniae</i>	<0.005	<0.005	0.008	<0.005
<i>C. Pneumoniae</i>	0.015	0.06	0.06	0.12

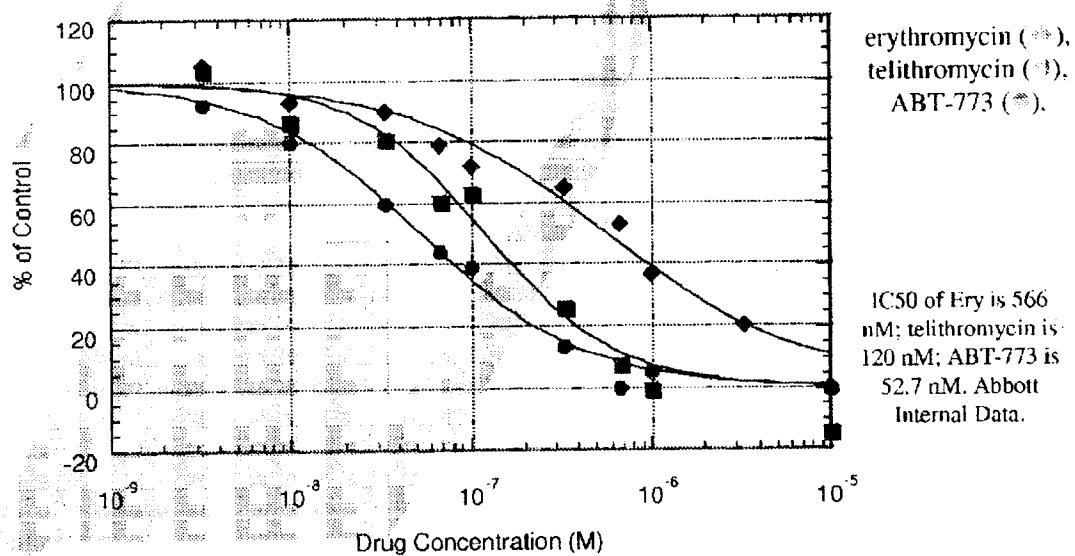


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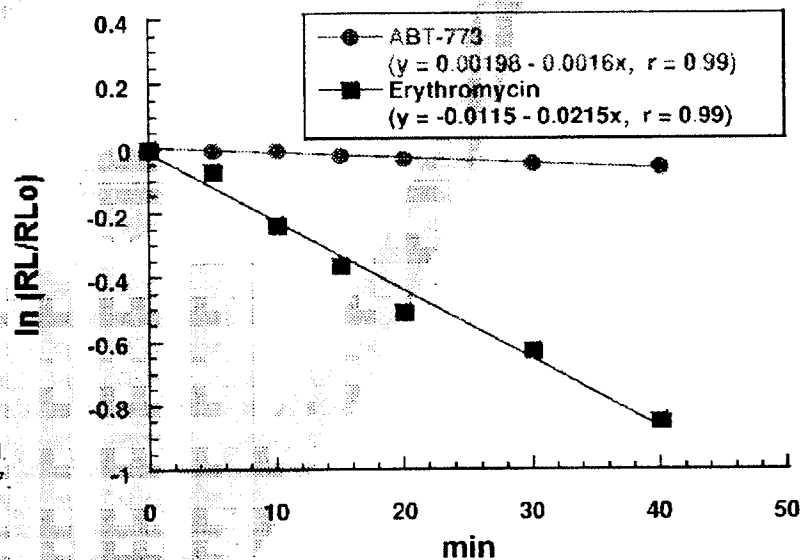


## Ribosome Binding, Susceptible *S. pneumoniae*

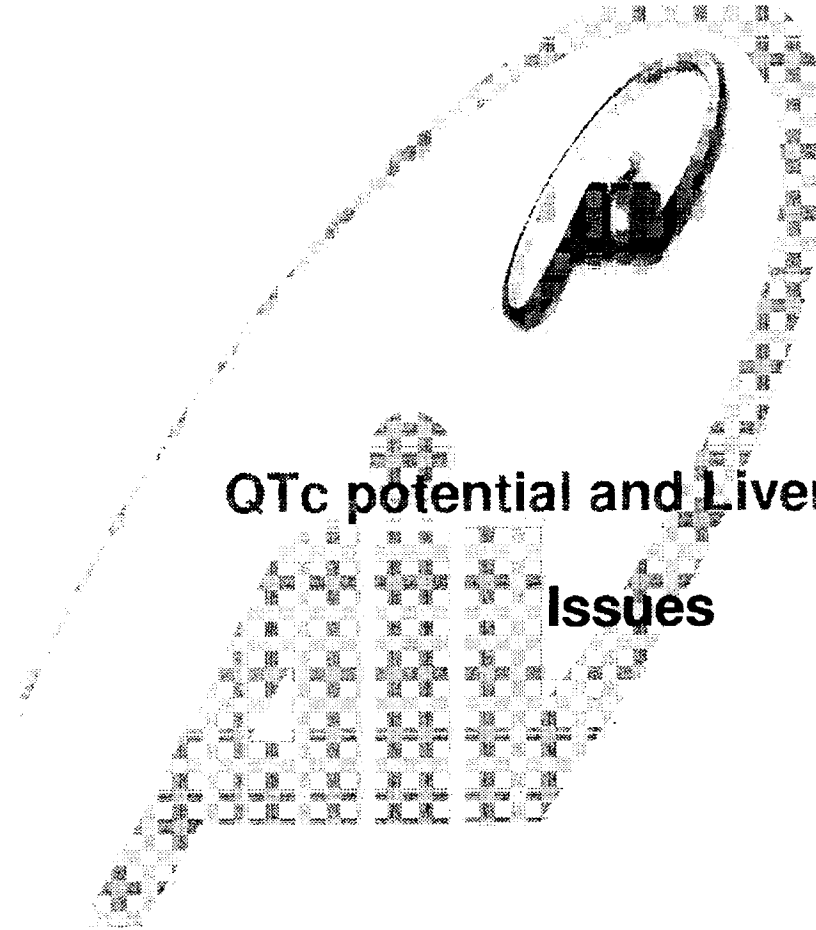




## ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.



# **QTc potential and Liver Toxicity Issues**

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ABBT205059





## QTc Prolongation Issues

- Potential for QTc Prolongation is a hot button worldwide
  - Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies
  - CPMP guidelines require data from animal models and 200 subjects
  - FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
  - FDA has question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QTc
  - Required to include ECG monitoring in pivotal Phase 3 studies
  - FDA may require a Phase I study in patients with underlying cardiac disease
  - Some antimicrobials now contain warnings for QT prolongation
  - Telithromycin (Ketek) data residing at FDA
    - Advisory Meeting rescheduled to May 2001 probably not related to QTc concerns



## QT<sub>c</sub> Prolongation Issues ABT-773

- Pre-clinical data positive for QT<sub>c</sub> dose response.
- A possible dose effect in Phase I at total daily dose  $\geq 800$  mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 C<sub>max</sub> 5X)
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)



## **QT<sub>c</sub> Prolongation Issues ABT-773 Plan**

- Completed pre-clinical evaluation of ABT-773
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QT<sub>c</sub> and electrolytes in Phase III programs.
- Planning FDA requested study of QT<sub>c</sub> in patients with pre-existing cardiac disease.
- IV ABT-773 Phase I study will monitor QT<sub>c</sub> carefully
- Consult with Drs. Morganroth and Moss QT<sub>c</sub> advisors.





## Liver Toxicity Issues

- **Potential for liver toxicity is a concern for the FDA**
  - Recent liver toxicity seen with Trovofloxacin are of concern to regulatory agencies.
  - Gemifloxacin recently not approved by FDA because of liver toxicity concerns.
  - FDA meeting on guides to industry on how to study liver function scheduled for February 11-12, 2001



## **Liver Toxicity Issues for ABT-773**

- Preclinical tox showed some effect on the liver function.
- Japanese in bridging study showed increased LFTs.
- No evidence of LFT issue in Western subjects.
- No evidence of dose response.
- Repeat of Japanese bridging study in Japan showed No evidence of LFT increases in Japanese or Caucasians.
- ABT-773 plan for accessing problem
  - Continue to monitor LFT in Phase III programs.
  - Jean Fox will attend FDA meeting.



# **Phase III Program**

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## Phase III Program

### Proposed Indications and Treatment Duration

Infection	Dosage	Duration
Pharyngitis/Tonsillitis due to:		
<i>S. pyogenes</i> *	150 mg QD	5 d
Acute bacterial sinusitis due to:		
<i>H. influenzae</i>	150 mg QD or BID	10 d
<i>M. catarrhalis</i>	150 mg QD or BID	10 d
<i>S. pneumoniae</i> **	150 mg QD or BID	10 d
Acute bacterial exacerbation of chronic bronchitis due to:		
<i>H. influenzae</i>	150 mg	5 d
<i>H. parainfluenzae</i>	150 mg	5 d
<i>M. catarrhalis</i>	150 mg	5 d
<i>S. pneumoniae</i> **	150 mg	5 d
Community-acquired pneumonia due to:		
<i>C. pneumoniae</i>	150 mg QD or BID	10 d
<i>H. influenzae</i>	150 mg QD or BID	10 d
<i>L. pneumophila</i>	150 mg QD or BID	10 d
<i>M. pneumoniae</i>	150 mg QD or BID	10 d
<i>S. pneumoniae</i> **	150 mg QD or BID	10 d

\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.



### Phase III Program Studies Started in Year 2000

Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	185/520	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	0/520	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	131/600	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	0/500	EU (Non-IND)

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**Phase III Program**  
***Studies Started in Year 2000, Con't***

**Dose Finding Studies for Sinusitis/CAP:**

<b>Study</b>	<b>Indication</b>	<b>ABT-773 Regimen</b>	<b>Comparator</b>	<b>Number Subjects</b>	<b>Location</b>
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	137/500	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	76/500	US, Canada, EU (IND)

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## Dosing Issue

### 150 mg BID vs 150 mg QD: Background

- Phase II data indicated 300 mg QD was not viable due to high levels of diarrhea (10-20%) and taste perversion (10-20%)
- Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD
  - 150 mg QD currently being evaluated in ongoing phase III trials in these indications
- Dosing selection for CAP and sinusitis confounded by limited data
  - few bacterial isolates, particularly with *H. flu* in sinusitis
  - no 150 mg arm in CAP trial
- To increase probability of correct dose selection in CAP/sinusitis, the decision was made to undertake additional studies to generate more data in these indications
  - 150 mg QD vs 150 mg BID CAP & sinusitis trials ongoing
  - Decision facilitated by Decision Support Group, with joint AI & PPD consensus on decision



## Dosing Issue

### 150 mg BID vs 150 mg QD: Implications of Decision

- **For U.S. market:**

- Absence of consistent QD dosing for all indications represents a significant commercial hurdle
- Approval on indication-by-indication basis
- Optimal strategy for U.S. may be to pursue QD dosing for CAP/sinusitis

- **For ex-U.S. market:**

- CAP data represents the "lynchpin" for approvability of the entire molecule, hence a conservative BID approach may result in lower regulatory/commercial risk
- Relatively minor commercial impact of BID dosing
- Optimal strategy for ex-U.S. may be to pursue BID dosing for CAP and perhaps sinusitis

- **A decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01**

- Key ex-U.S. criteria for CAP approval include: a) satisfactory efficacy/eradication in severe CAP b) sufficient resistant isolates with satisfactory eradication c) treatment of bacteremic cases
- data may not show a clear "winner" due to relatively low power of studies; may be a difficult decision
- due to soft global flu season and protocol amendments, enrollment is behind plan and could impact timing of decision

- **A plan to have divergent clinical programs in CAP/sinusitis may be an option**

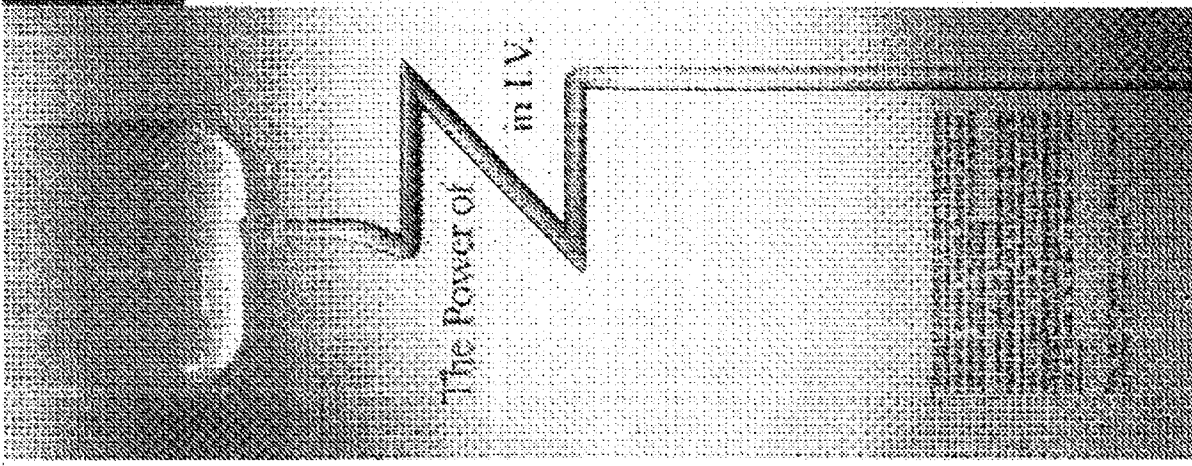




# **ABT-773 IV Program**

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ABBT205071



**The Power of Z in I.V.**

**Once-daily  
Zithromax I.V.**  
*azithromycin for injection*

The only I.V. azithromycin formulation  
indicated for community-acquired  
pneumonia in adult hospitalized patients.

The potent coverage of the key pathogens of  
community-acquired pneumonia.

Times	Aspirin
Single-dose penicillin	Single-dose penicillin
Single-dose ampicillin	Single-dose ampicillin
Single-dose ceftriaxone	Single-dose ceftriaxone
Single-dose vancomycin	Single-dose vancomycin

Proven to achieve 100%  
culture-negative rates.

Early step-down therapy to oral Zithromax.  
You'll see it reflected.

As soon as you're able to tolerate oral intake,  
switch to oral Zithromax. It's the only I.V. azithromycin  
formulation that can be safely and effectively  
switched to oral therapy. No need for a second  
course of therapy.

For more information, visit us online at  
[www.zithromax.com](http://www.zithromax.com) or call 1-800-441-4411.

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[www.zithromax.com](http://www.zithromax.com) or call 1-800-441-4411.

# PART 4



## ABT-773 IV Formulation Strategic, Commercial, and Technical Value

- Strategic Value
  - IV represents a channel not currently served by Anti-infective Franchise
  - Leverages presence of Medical Center Reps and experience with ID community
- Commercial Value
  - IV availability figures favorably into decisions regarding formulary access to molecule
    - potential advantage over telithromycin, which will not have an IV
    - required to compete effectively with Zithromax, Tequin, Avelox which have IVs
  - Positive impact on tablet formulation
    - estimated \$36MM incremental to peak tablet sales due to step-down therapy
    - Enhances overall "potency" image of brand
- Technical Value
  - Support for *S. pneumoniae* Resistance claim
    - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
  - Provides additional information on QT effects

IV launch currently lags tablet launch by 1 year; any further delays will reduce the potential value



## **ABT-773 IV Program Formulation Objectives**

- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counter ion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.



## **ABT-773 IV Formulation PPD/HPD Funding Status**

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV (\$7MM)
  - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)



## **ABT-773 IV Formulation**

### ***Animal Pain Study Results***

- Assessed 6 prototypes (3 different counter ions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
  - Results not conclusive
  - Need to evaluate in humans
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.



## **ABT-773 IV**

### **Planned Clinical Program**

*With 2001 funding decision in Feb:*

- |  |         |
|--|---------|
| • Single Dose-rising Phase I study         | Apr/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND                              | Oct/01  |
| • Initiate Phase III                       | Dec/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |

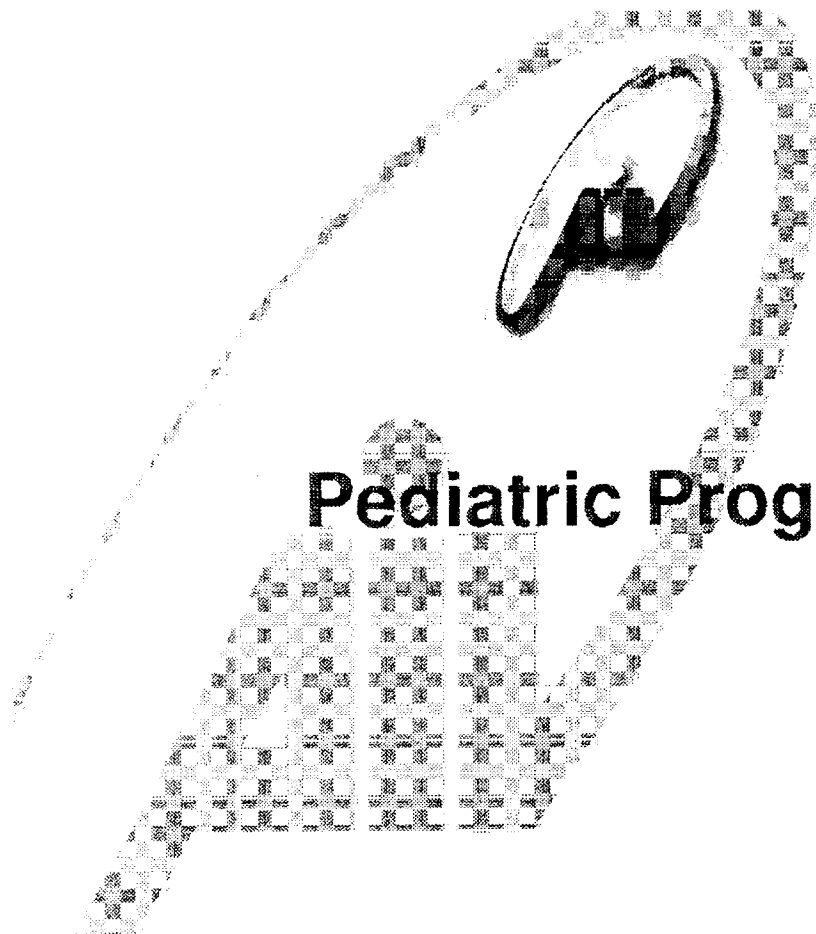




## ABT 773 IV Program Summary

- **Comments**

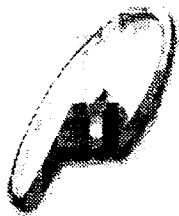
- Funding for '01 not available PPD/HPD
- Go/No go could be made after Phase I based on safety profile (pain,QT,GI)
- Milestone funding recommended (\$1MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant *S. pneumo* claim
- Total Program Cost 2000-2003 (\$22.5MM)



## Pediatric Program

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ABBT205079



## **ABT-773 Pediatric Formulation**

### **Importance to the 773 program**

- Increased perception of safety
- Better pricing and acceptance in European markets
- FDA requires studies in pediatrics



## **ABT-773 Pediatric Program Formulation Objectives**

- Develop coated particle formulae for global use
  - coated particles for Suspension - 150mg/5mL & 300mg/5mL
  - coated particles as a dry syrup, sprinkle or sachet.
- Desired Properties
  - Once a Day Dosing
  - Acceptable 'Initial Taste'
  - Minimal 'After Taste'
  - No Unpleasant Mouth-feel
  - Acceptable Color and Flavor
  - No Refrigeration Required.



## ABT 773 Pediatric Program Taste Assessment

### Sensory Analysis of Uncoated Drugs *Summary of Results*

The three drug substances can be ranked from most to least bitter as follows:

Drug Substance	Concentration (ppm) Which Exhibits an Initial Bitter Intensity <1 (Slight)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

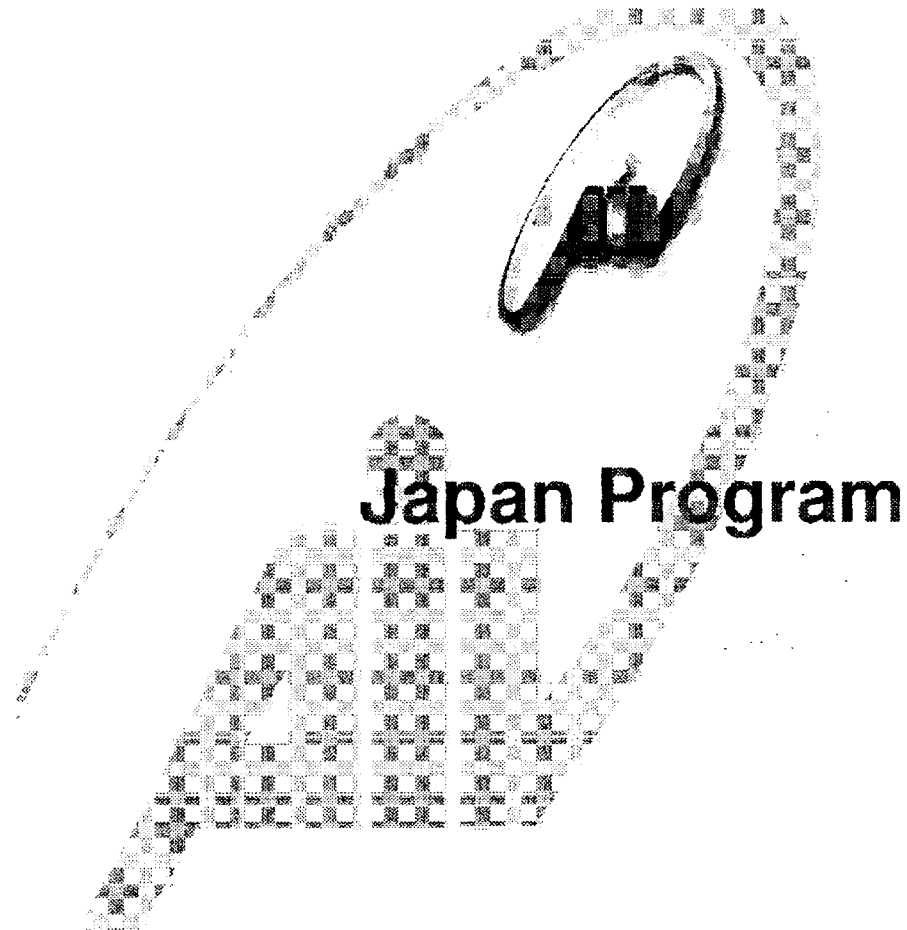
- ABT-773 is approximately five times more bitter than clarithromycin



## **ABT 773 Pediatric Program**

### ***Taste Assessment***

- The ABT-773 encapsulated prototype #2 may be at risk of dosing compliance problems due to flavor quality.
- Overall ABT-773 Prototype 2
  - Less bitter than Biaxin both initial and after taste
  - More bitter than Zithromax both initial and after taste
- For ABT-773 Prototype 2, the flavoring aromatics and sweetness decay quickly, exposing the bitterness which lingers throughout the aftertaste at or above the “concern” intensity level.



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## Japan Program Taisho

- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan





## Japan Program Clinical Plan

- Phase I in Japan
  - Food Effect Study Start  
Completed
  - Single and multiple dose study Completed
  - Review data (Abbott/Taisho) April/01
    - PK data Japanese vs Caucasian
    - Development program strategy
  - Present Kiko data and recommend development program 
    - May/01
  - Start Tissue Conc. Study 2Q/01

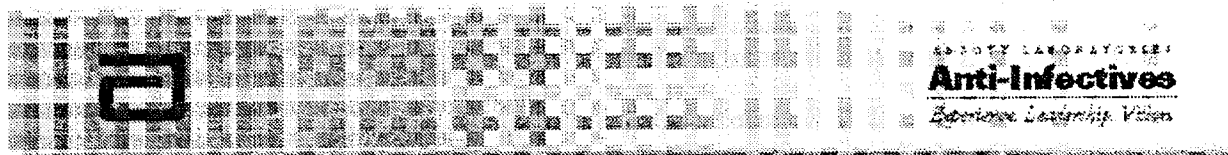


## Japan Program Clinical Plan

- PK similar in Japanese and Caucasians (12/02 filing)
  - Recommend to Kiko same dose in Japan as in ex-Japan
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in skin infections, dentistry, otolaryngology, UTI and pan-bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians (12/03 filing)
  - Phase II dose ranging study in CAP (Bridging study)
  - Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing

**ABT-773 Portfolio Review**  
December 5, 2000

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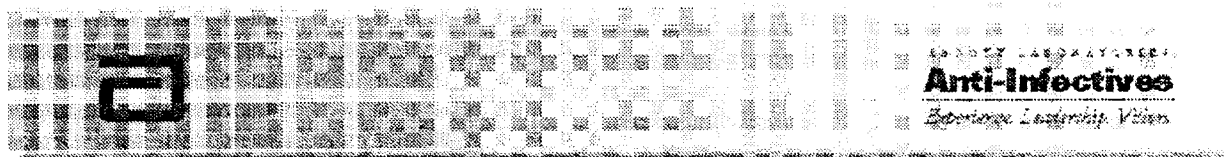
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ABB T205088

## *Agenda*

*Part 1: General Overview, Tablet*

- 
- **Introduction-Carl Craft (5 min)**
  - **Executive Summary-George Aynilian (10 min)**
  - **Anti-Infective Market/Commercial Rationale-Rod Mittag (15 min)**
  - **Microbiology-Bob Flamm (20 min)**
  - **Tablet Clinical Program**
    - Phase II data-Joaquin Valdes (20 min)
    - Phase III clinical plan-Joaquin Valdes (10 min)
  - **SPD Summary-Ashok Bhatia (10 min)**
  - **Tablet Key Issues**
    - Analysis of QT/Liver data-Dave Morris (20 min)
    - PK profile-Linda Gustavson (10 min)
    - Regulatory-Jeanne Fox (10 min)
    - Timeline risk George Aynilian (5 min)
  - **Tablet Commercial Profile, Strategy & Financials-Rod Mittag (10 min)**



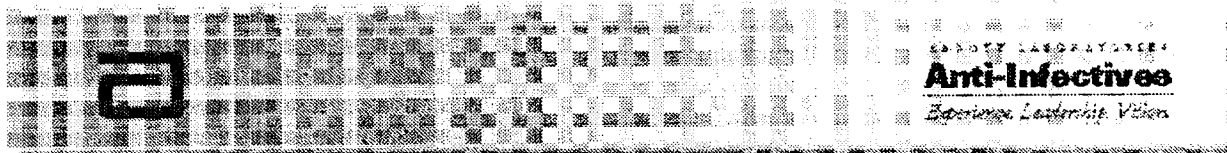
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## Agenda

Part 2: I.V., Pediatric, Japan, Q&A

- 
- I.V. Program/Issues-Carol Meyer (5 min)
  - Pediatric Program/Issues-Carol Meyer (5 min)
  - Japan Program/Issues-Carol Meyer (5 min)
  - ABT-492 (time permitting)
    - timeline
    - budget
    - rationale
  - Summary-Carl Craft (5 min)
  - Q&A

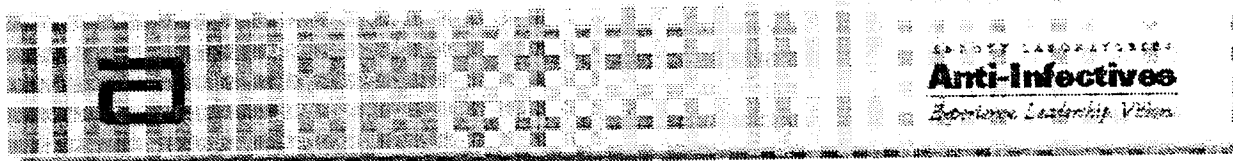


**ABT-773*****Executive Summary***

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- **Management**

- Established European Clinical Team (11 dedicated members)
- Plans ongoing to strengthen Japan team
- Completed staffing of Abbott Park team
- Established communication team
- Completed conceptual model of study tracking application (web based)
- Established integrated project management system



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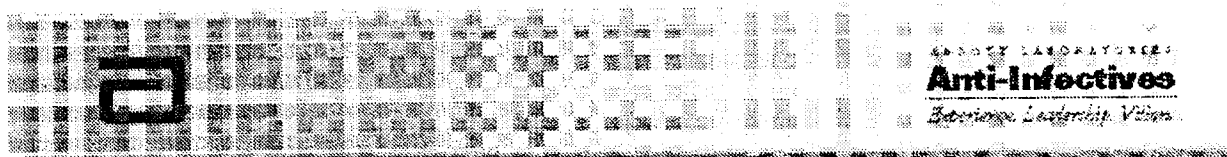
ABBT205091

**ABT-773*****Executive Summary***

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- **Chemistry**

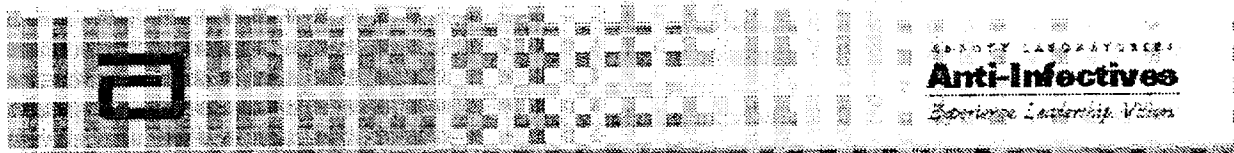
- Exceeded '00 goals for yield, cost/Kg and deliveries
- Task Force implemented modification of 3 steps
- 3 TPMs for intermediates well established
- Prepared package for justifying Step 5 as starting material



**ABT-773**  
*Executive Summary*

---

- **Tablet Formulation**
  - Scale up operations at AP and IDC on target
  - Linkage of materials between scales and sites being established by bioequivalency trials.
  - NDA runs and stability were initiated for 08/02 filing.



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ABBT205093



**ABT-773*****Executive Summary***

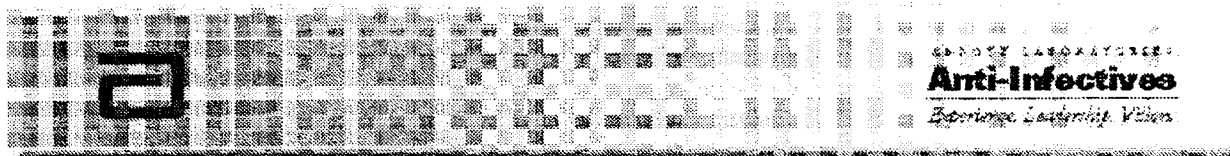
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- **IV Formulation**

- Clinical supplies complete. Tox. program ongoing. Phase I planned for 1Q '01.

- **Pediatric formulation**

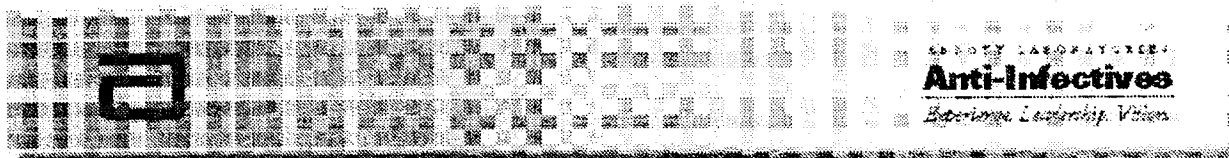
- Phase I complete with two prototypes. After- taste an issue. Formula optimization required. Pro-drugs under consideration. No funding in '01 plan budget



**ABT-773*****Executive Summary***

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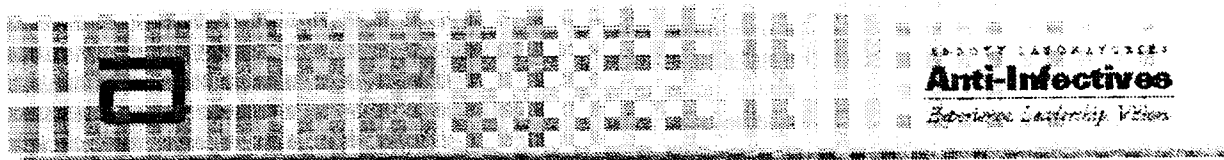
- **Preclinical Safety**
  - Dog model (IV infusion) and Purkenje fiber studies completed as part of effect of drug on QTc. Additional study planned per EOPII meeting with FDA.
- **Molecular Biology**
  - Extensive work on ribosomal binding completed. Preliminary results published. Additional studies ongoing.



## **ABT-773**

### **Executive Summary**

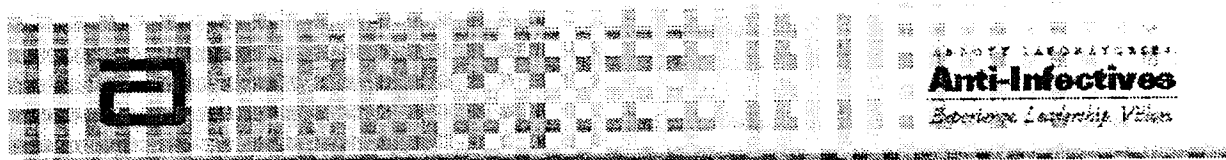
- 
- **Clinicals**
    - Completed Three Phase IIb studies
    - Decision Support Analysis completed
    - Dose selection 150mg and 150mg bid
    - Initiated Phase III program( 6 studies, 4 under IND)
    - Completed all Investigator's meetings
    - Regulatory meetings
      - UK, Germany, France, US
  - **End of Phase II package**
    - Document sent to FDA X/X
    - End of phase II meeting held with FDA 11/26
  - **Japan bridging study/Kiko Mtg/Repeat Phase I in Japan**



**ABT-773**  
*Executive Summary*

---

- **Key Events (Nov '00-June '01)**
  - Initiate Phase III (ABECB, ASP, ABS, CAP) in US/EU
  - End of Phase II meeting with FDA (New amendment, informed consent)
  - Initiate Japan Phase I program in Japan
  - Results of Phase III (CAP/ABS) studies
  - Selection of regimen between 150mg QD and 150mg BID for CAP/ABS.
  - Set up balance of Phase III studies (CAP/ABS) 4 studies

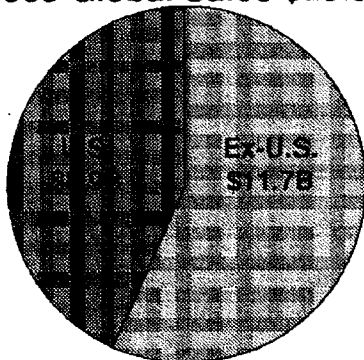


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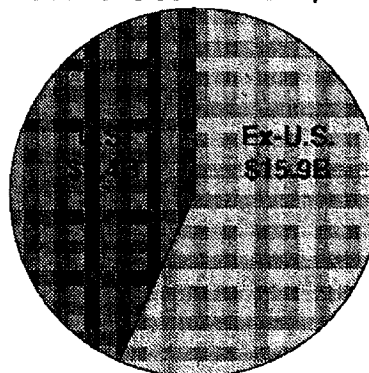
ABBT205097

**Global Antibiotic Market Sales**  
*Current vs Future Projection*

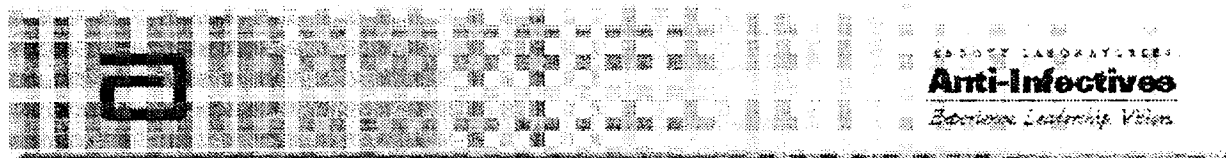
**1999 Global Sales \$20.6B**



**2005 Global Sales \$25.3B**

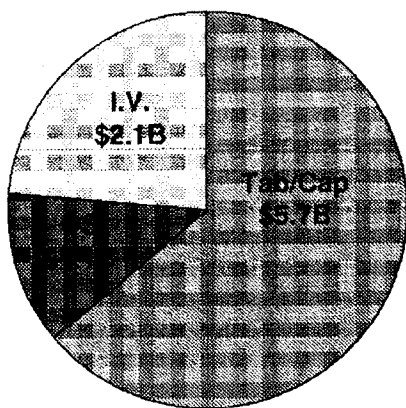


The antibiotic market is a large market and is expected to expand on a global sales basis

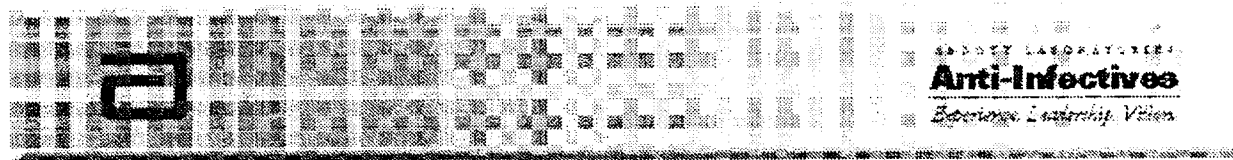
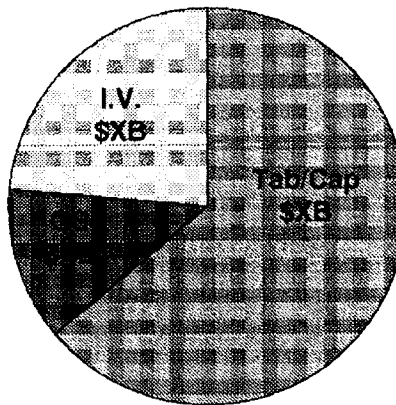


**Global Antibiotic Market Sales**  
by Formulation

1999 U.S. Sales \$8.9B



1999 Ex-U.S. Sales \$11.7B



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ABB1205099

## Key Competitors

## U.S. Market

Franchise	Macrolides	Quinolones	Beta-Lactams	Other	Infectables
Abbott	\$956	\$740	\$46	\$3	\$165
Pfizer	\$1,366	\$1,078	\$71	\$3	\$213
SB	\$1,303		\$1,229		\$74
Bayer	\$1,004		\$911	\$1	\$122
J&J	\$797		\$612		\$165
Hoeche	\$525			\$10	\$119
Glaxo	\$551	\$6	\$425	\$28	\$92
BMS	\$387	\$1	\$386		
Lilly	\$107		\$33		\$74
Others	\$1,670	\$95	\$27	\$631	\$298
'99 Total	\$8,790	\$1,911	\$1,628	\$2,755	\$343
'96 Total	\$7,570	\$1,582	\$1,331	\$2,453	\$272
% Chg	16.12%	20.04%	22.31%	12.31%	26.10%
TY vs LY					
* Includes IV form of all classes					
Source: IMS					

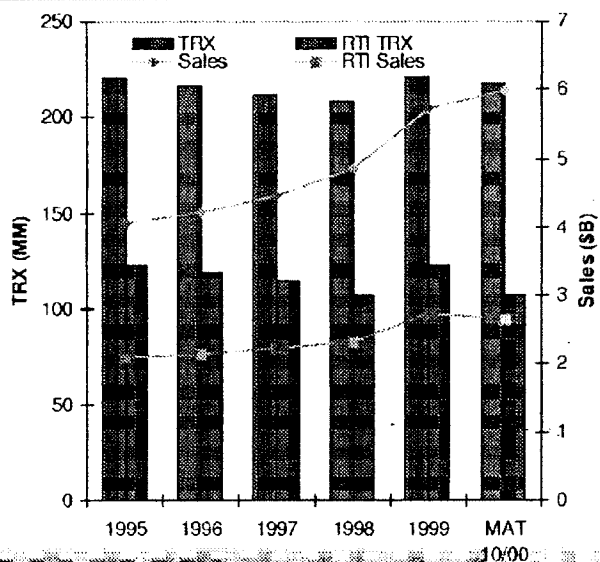
## Ex-U.S. Market

Franchise	Macrolides	Quinolones	Beta-Lactams	Infectables	Other
Abbott	\$ 717	\$679	\$ 22	\$ 3	\$ 13
Shionoi Seiyaku	\$ 969	\$ 2	\$ 3	\$ 432	\$ 466
Pfizer	\$ 654	\$262	\$ 12	\$ 68	\$ 246
SKB	\$ 842	\$ 0	\$ 0	\$ 780	\$ 61
BMS	\$ 547	\$ 0	\$ 2	\$ 378	\$ 154
Roche	\$ 460	\$ 0	\$ 3	\$ 43	\$ 303
Bayer	\$ 524	\$ 0	\$487	\$ 43	\$ 43
Lilly	\$ 437	\$ 28	\$ 0	\$ 337	\$ 66
Fujisawa Yakuhin	\$ 522	\$ 0	\$ 0	\$ 411	\$ 111
Daiichi Seiyaku	\$ 487	\$ 0	\$487	\$ 0	\$ 0
'99 Sub-total	\$6,176	\$977	\$976	\$2,495	\$1,461



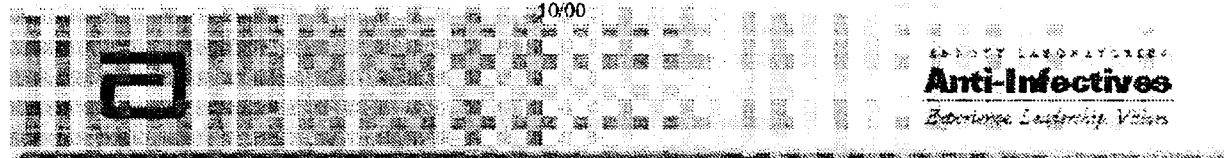
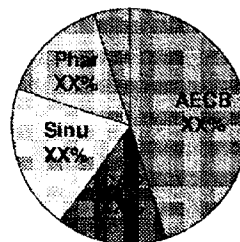
DAIICHI SEIYAKU  
**Anti-Infectives**  
*Excellence. Leadership. Vision.*

### U.S. Tab/Cap Antibiotic Market TRX & Sales Trends



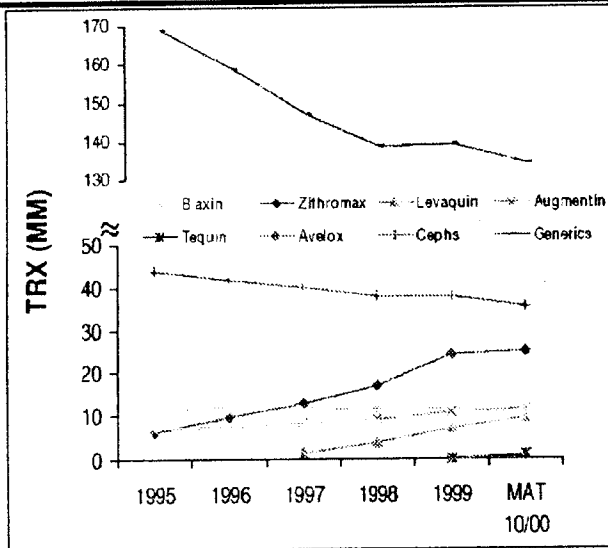
- While negative pressure exists on antibiotic usage, market sales have increased substantially
- TRX CAGR<sub>95-99</sub> = + 0.1%
- Sales CAGR<sub>95-99</sub> = + 8.9%

#### RTI Sales by Indication





### U.S. Tab/Cap Antibiotic Market Product Trends

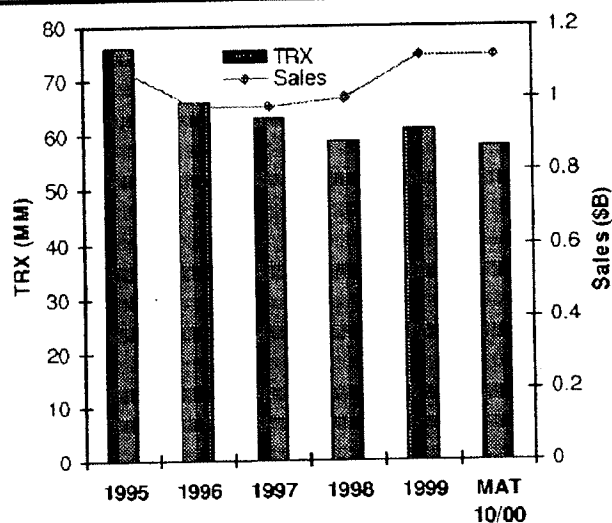


- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Zithromax has driven market demand for cost/convenience/tolerability
- Quinolones (Levaquin, Tequin, Avelox) are fastest growing segment, playing into resistance concerns; 1998-99 growth of 15% (TRX) & 22% (\$)



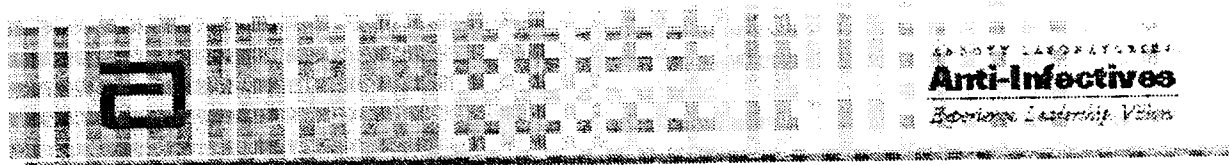
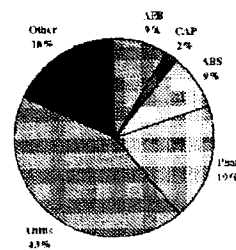
**Anti-Infectives**  
Boehringer-Ingelheim

### U.S. Pediatric Antibiotic Market TRX & Sales Trends



- TRX CAGR<sub>95-99</sub> = - 5.4%
- Sales CAGR<sub>95-99</sub> = + 1.0%
- TRX under greater pressure than Tab/Cap market
- Recent leveling in sales

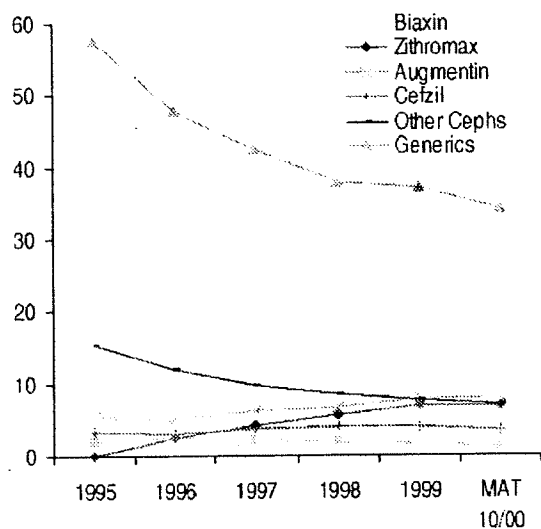
Sales by Indication



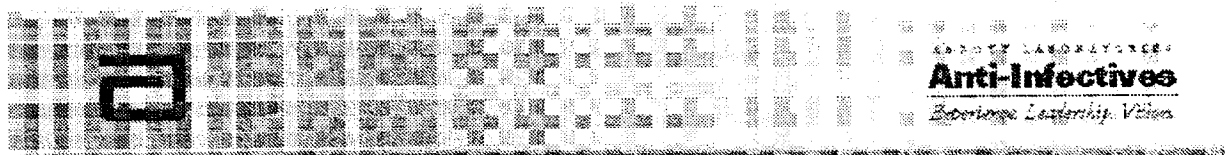
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ABBT205103

### U.S. Pediatric Antibiotic Market Product Trends



- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Taste and convenience are key market drivers
- Key branded products (Zithromax, Cefzil) lose patent exclusivity in 2005 timeframe
- May be opportunity for ABT-773, as resistance is substantial in this population; also conveys positive "safety" image to brand

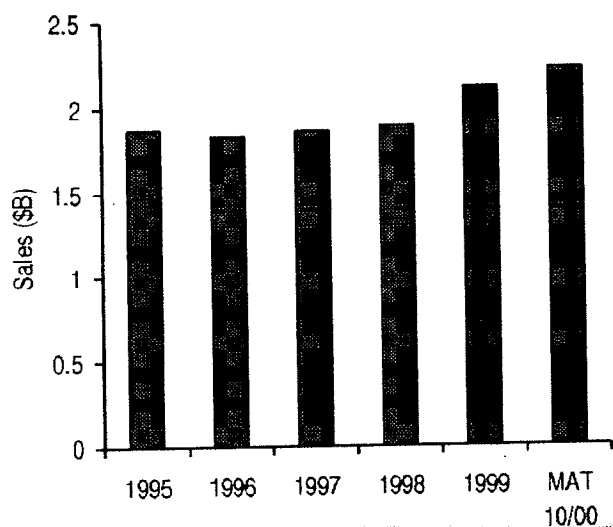


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ABB T205104

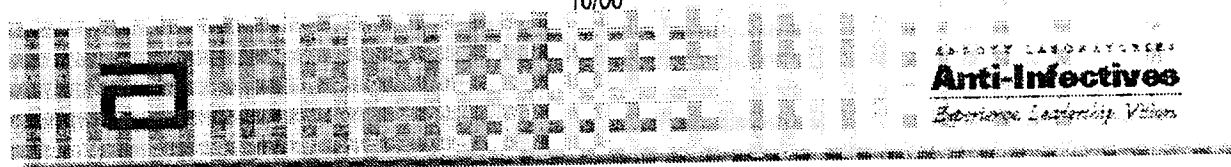
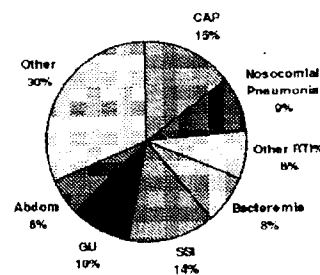
# PART 5

## U.S. Injectable Antibiotic Market Sales Trends



- Current Market: \$2.1B, CAGR = + 3.2%
- Two market segments:
  - Severe community-acquired
    - Rocephin, Levaquin, Tequin, Zithromax
  - Nosocomial
    - Synercid, Zyvox, vancomycin

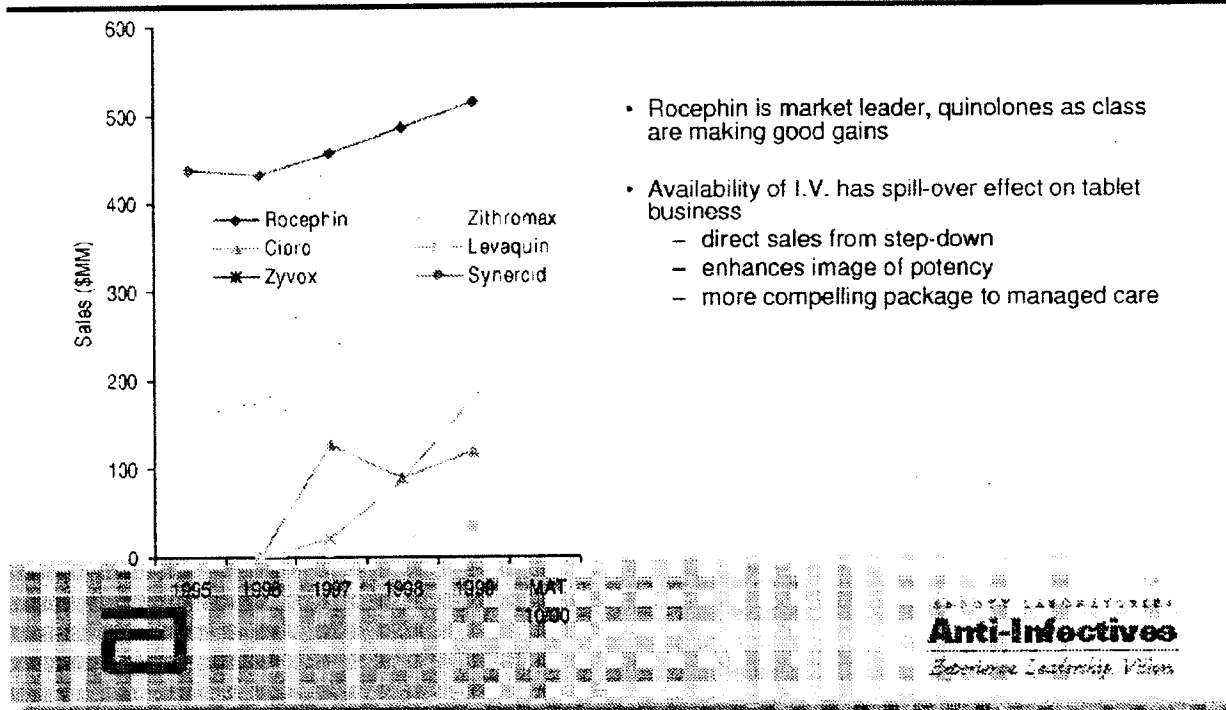
### Uses by Indication



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ABBT205105

### U.S. Injectable Antibiotic Market Product Trends



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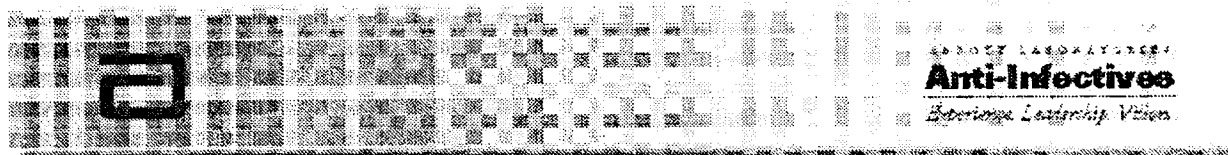
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## Global Market Drivers

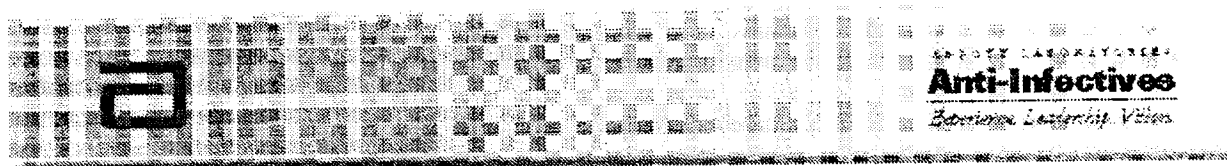
### Negative vs Positive Drivers

- Antibiotic Resistance
  - Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓
  - Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑
- Patent Expirations
  - May increase price sensitivity and bargaining power of MCOs ↓
  - Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑
- Market expansion ex-US ↑
- Unmet Need ↓
  - Overall unmet need relatively low
  - Cost, convenience, tolerability take on added importance
  - Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics
- Competition ↓
  - 5 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox
  - Continued discovery/development activity by key competitors
  - High level of promotional activity

Negative driver ↓  
Positive driver ↑



- 
- Resistance surveillance



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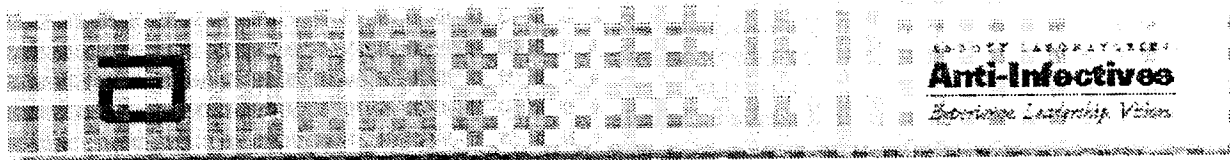
ABB1205108



**Patent Expirations**  
*Expiration & At Risk Sales*

	<u>Year</u>	<u>1999 U.S. Sales</u> <u>(\$MM)</u>
Ceftin	2003	\$425
Cipro	2003	\$1,023
Biaxin	2005	\$756
Cefzil	2005	\$357
Levaquin	2005	\$708
Zithromax	2005	\$1,111

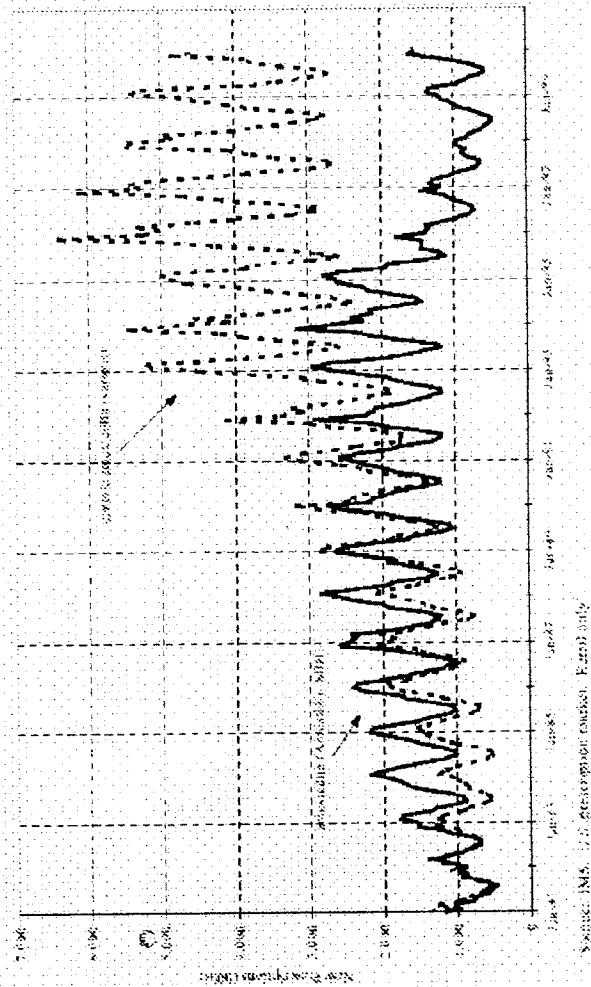
\$5,540



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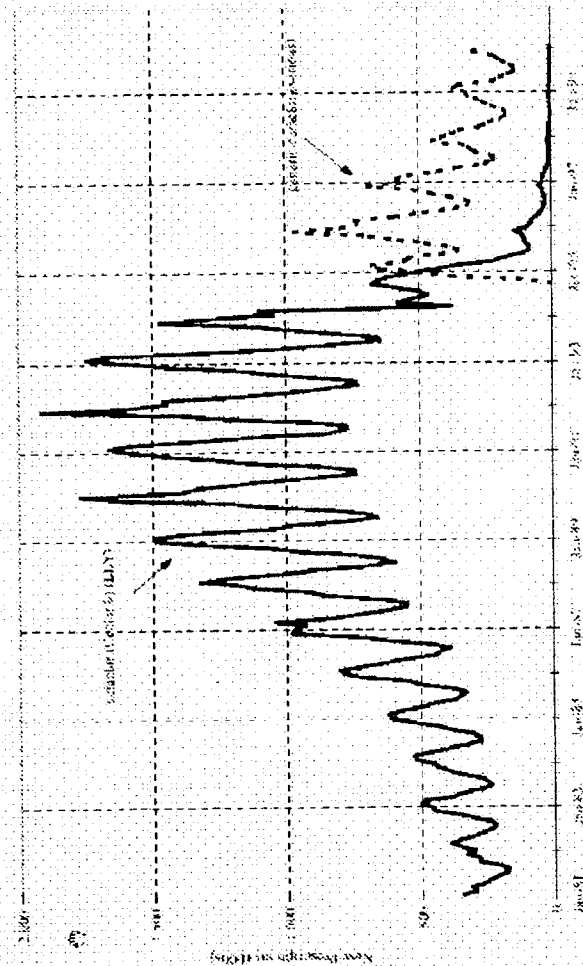
ABBT205109

Figure 139. SBT's Amoxiclo vs. generic amoxicillin, 1991-2000 (New Prescriptions, monthly data)



LABORATORIES  
**Anti-Infectives**  
*Expanding Leadership Vision*

Figure 140. Lilly's Ceftazidime vs. generic cefazidime, 1981-2000 (New Prescriptions, monthly data)

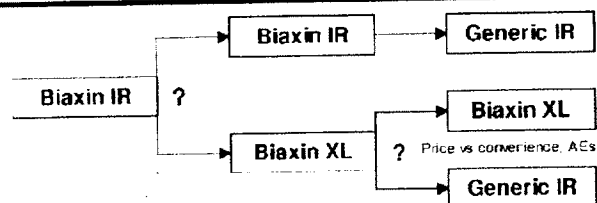


Source: IMS, U.S. prescription market, Retail sales

ABBOTT LABORATORIES  
**Anti-Infectives**  
*Experience Leadership Years*

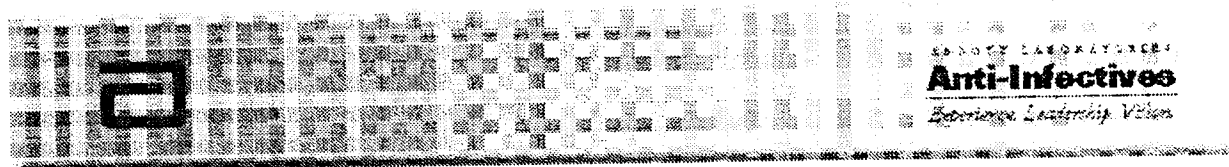
## Biaxin Patent Expiration

### Biaxin/773 Scenarios



		XL==> Generic Conversion		
		Low	Med	High
IR ==> XL Conversion	Low	?	C	C
	Med		?	C
	High			?

C = Convert Biaxin to ABT-773  
Assumes high conversion rate of IR to generics

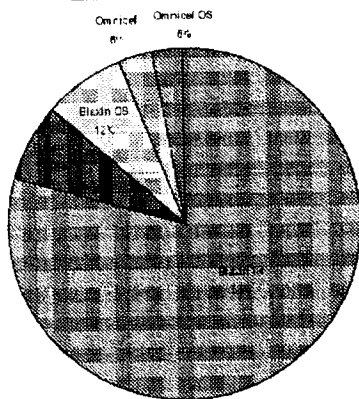


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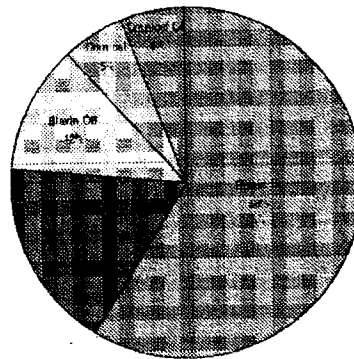
ABBT205112

**Abbott Anti-Infective Franchise**  
2001 Plan

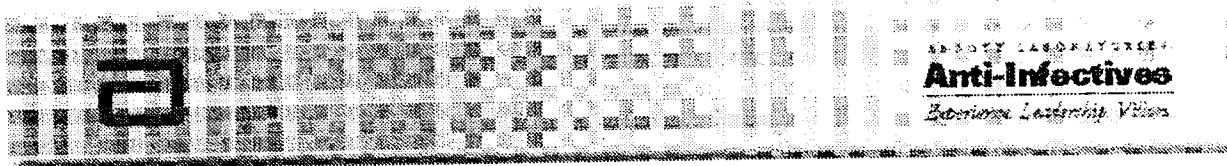
U.S. Sales = \$794 MM



Ex-U.S. Sales = \$XXX MM



The global Anti-Infective portfolio is heavily dependent upon Biaxin; ABT-773 represents a key program given the Biaxin patent expiration in 2005

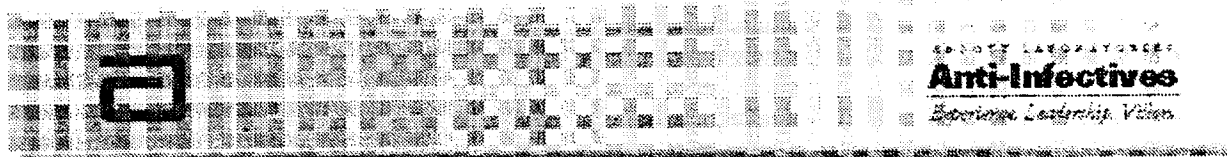


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ABBT205113

**ABT-773 Profile**

	Current Profile
Dosing	150 mg QD x 5 d for ABECB & pharyngitis (1-pack) 150 mg QD or BID x 10 d for CAP & ABS (2-pack if QD)
Efficacy	ABECB: 87% Cure, 86% Eradication (150 mg QD) ABS: 89% Cure, 77% Eradication (150 mg QD) CAP: XX% Cure, XX% Eradication (300 mg QD) Pharyngitis: No clinical data, need > 85% for indication
Adverse Events (150 mg QD)	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%
Resistance Claim	Being pursued, dependent on resistance prevalence/recovery/efficacy & availability of I.V.

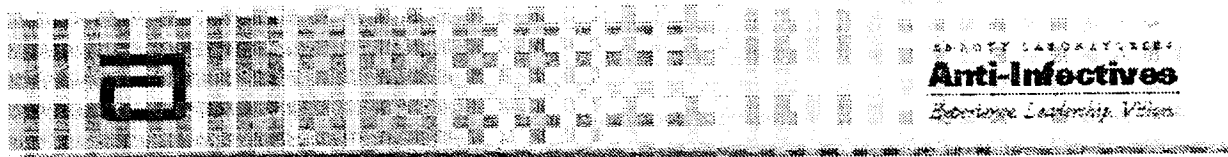


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ABBT205114

**ABT-773 Profile**  
vs Biaxin XL

	ABT-773	Biaxin XL
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: 6% Diarrhea: 6% Nausea: 3% Vomiting: 1%
Resistance Claim	Being pursued	Under exploration



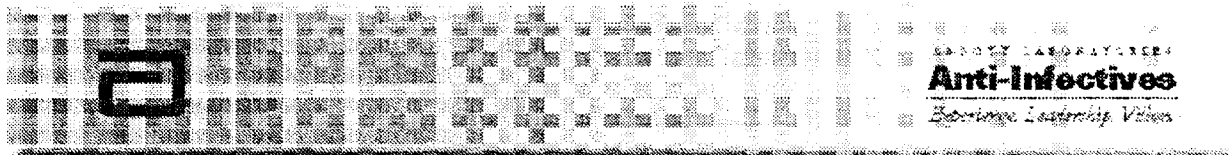
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ABB1205115

### ***Key Commercial Challenges***

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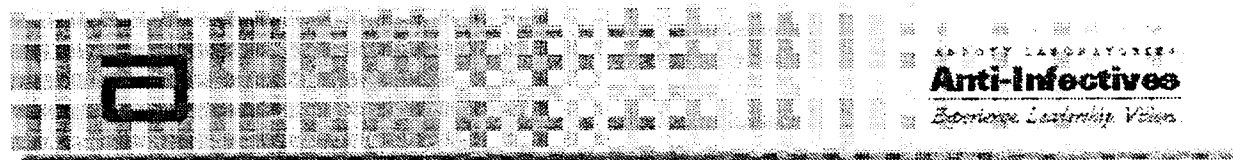
- **150 mg QD vs 150 mg BID**
  - 150 mg QD may prove efficacious in CAP/ABS ==> uniform QD dosing; however, limited 150 mg QD data currently exists, hence risk of BID dosing for CAP/ABS
  - Even if 150 mg QD efficacious, this regimen could receive regulatory challenge, particularly among ex-U.S. agencies==> QD and BID development programs, increased cost
- **PK**
  - Negative implications for efficacy as well as resistance development
- **H. flu eradication**
  - dose-defining pathogen, limited number of data points to date
  - a strength of quinolones
- **Tolerability may be sub-optimal**
  - diarrhea and taste perversion
- **2nd to market ketolide**
  - Aventis ketolide Ketek (telithromycin), FDA advisory 1/29





**Phase II Data: 150 mg QD vs 300 mg QD**

		Phase IIb Data: Intent-to-treat							
		Bronchitis		CAP		Sinusitis		Total	
Clinical Cure	150 mg QD	85%	104/123			82%	72/88	83%	176/211
	300 mg QD	83%	107/129	84%	80/95	80%	72/90	82%	159/314
Bacteriological Cure	<i>H. flu</i>	150 mg QD	89%	17/19		60%	3/5	83%	20/24
		300 mg QD	81%	17/21	100%	9/9	100%	89%	33/37
	<i>S. pneumo</i>	150 mg QD	77%	10/13		100%	3/3	81%	13/16
		300 mg QD	90%	9/10	82%	14/17	100%	89%	31/35



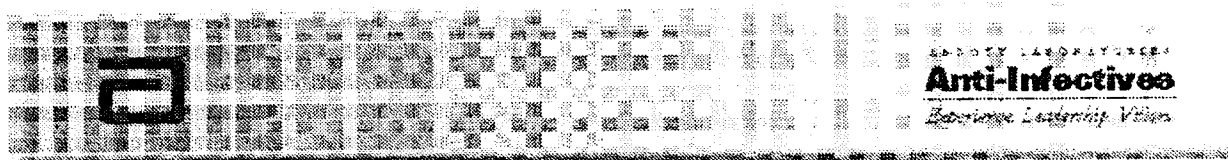
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ABB205117

### **Ketek Summary** *Regulatory Status*

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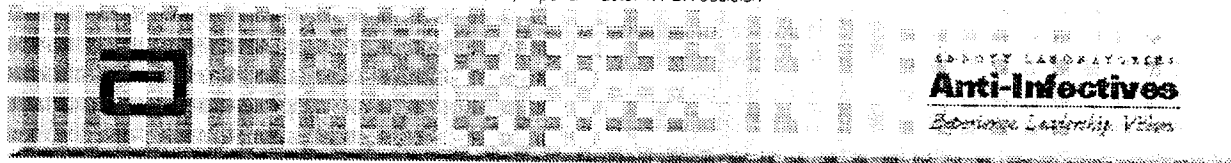
- Ketek (telithromycin, Aventis) will be first-to-market ketolide
- U.S.
  - Filed with FDA March 2000
  - **FDA advisory 1/29**
  - Expected approval 1Q01
- Ex-U.S.
  - Package submitted to EMEA as centralized filing in March 2000
    - Rapporteur = Sweden
    - Co-rapporteur = Portugal
    - Expected approval 1Q01
- Phase II in Japan (source: IMS World R&D Focus)



## Ketek Summary

### Profile Summary

- 
- 800 mg QD for all indications
  - AECB (5d), CAP (7-10d), sinusitis (5d), pharyngitis (5d)
  - High rate of diarrhea (10-20%) nausea (10%), but no taste perversion
    - statistically greater diarrhea vs trovafloxacin in phase III study
  - Comparable levels of efficacy to comparators (see appendix for full clinical summary):
    - 74%-95% clinical cure
    - 69%-94% overall eradication
    - H. flu eradication is varied, with two CAP studies having 75% and 78% eradication; an AECB and sinusitis study had H. flu eradication of 88% and 100% respectively
  - Liver function elevation
    - mentioned at ICAAC99, but Aventis claimed no clinically relevant impact at ICAAC2000; a CAP study references a 11.3% incidence of abnormal liver function, though the severity is unknown
  - QTc prolongation: Aventis maintains no clinically relevant impact
  - High COGS based on SPD pricing on intermediate
    - estimated telithromycin bulk drug cost of ~\$6,000/kg at launch vs \$3,000 for /r/3 at launch
    - may limit pricing flexibility
  - Competitive intelligence suggests 14 penicillin resistant isolates submitted, same number as Levaquin (potential for pen-resistance claim, which Levaquin was granted)
    - eradication rate with these isolates unknown, important factor in FDA decision

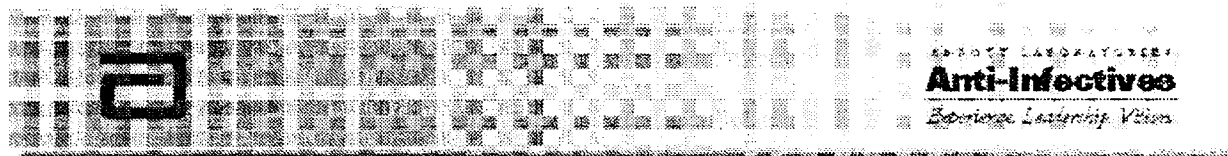


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ABBT205119

**Ketek Summary**  
**ABT-773 Comparison**

	<b>ABT-773</b>	<b>Ketek</b>
<b>Dosing</b>	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 400 mg QD ABECB: 5 d Phar: 5 d CAP: 7-10 d ABS: 10 d (or 5 d?)
<b>Efficacy</b>	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 86-89% Cure, 69-88% Erad ABS: 76-91% Cure, 86-91% Erad CAP: 91-93% Cure, 86-94% Erad Phar: 93-95% Cure, 84-91% Erad
<b>Adverse Events</b>	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: Not reported Diarrhea: 10-20% Nausea: 10% Liver, QTc: ???
<b>Resistance Claim</b>	Being pursued	Submitted in NDA



Confidential

ABBT205120

## ***Ketek Summary***

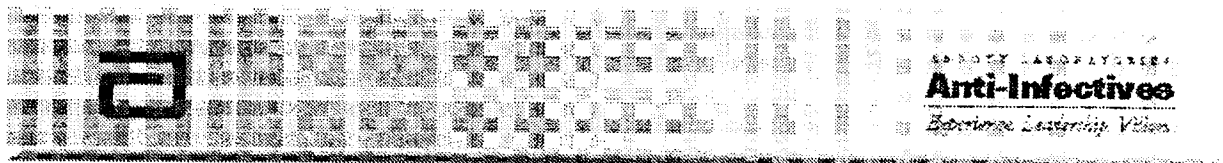
### ***ABT-773 Strengths/Weaknesses***

#### ABT-773 Strengths vs Ketek

- ABT-773 is considerably more potent than telithromycin against:
  - resistant and susceptible strains of *S. pneumo*
  - atypicals
  - H. flu (based on in vivo animal models)
- Lower rate of adverse events, particularly diarrhea
- 1 tab per dose vs 2
- Mechanistic advantages
  - faster binding to ribosome, slower release from ribosome, perhaps additional binding site(s)
- Potential for greater pricing flexibility

#### ABT-773 Threats/Issues vs Ketek

- 2nd to market
- Potential for BID dosing in CAP and/or sinusitis
- ABT-773 clinical/safety data at 150 mg QD based on relatively few data points
- PK profile



## Ketek Summary

### Clinical Data

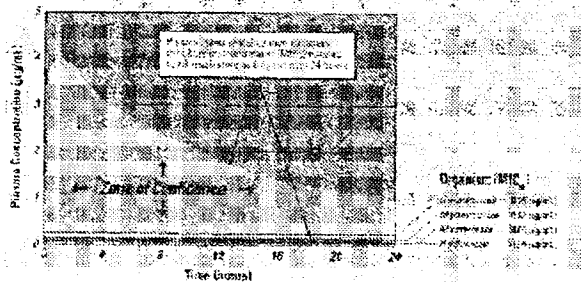
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2005	2.5	2.5
2006	2.5	2.5
2007	2.5	2.5
2008	2.5	2.5
2009	2.5	2.5
2010	2.5	2.5
2011	2.5	2.5
2012	2.5	2.5
2013	2.5	2.5
2014	2.5	2.5
2015	2.5	2.5
2016	2.5	2.5
2017	2.5	2.5
2018	2.5	2.5
2019	2.5	2.5
2020	2.5	2.5
2021	2.5	2.5
2022	2.5	2.5
2023	2.5	2.5
2024	2.5	2.5
2025	2.5	2.5
2026	2.5	2.5
2027	2.5	2.5
2028	2.5	2.5
2029	2.5	2.5
2030	2.5	2.5
2031	2.5	2.5
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2092	2.5	2.5
2093	2.5	2.5
2094	2.5	2.5
2095	2.5	2.5
2096	2.5	2.5
2097	2.5	2.5
2098	2.5	2.5
2099	2.5	2.5
2100	2.5	2.5

**Anti-Infectives**  
*Barrier Leadership. Value.*

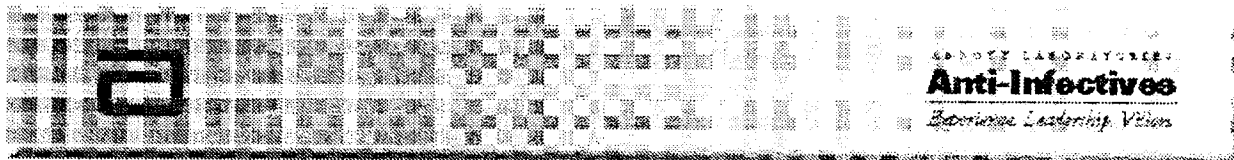
PK Issue

**AVELOX provides a 24-hour Zone of Confidence covering key respiratory pathogens**

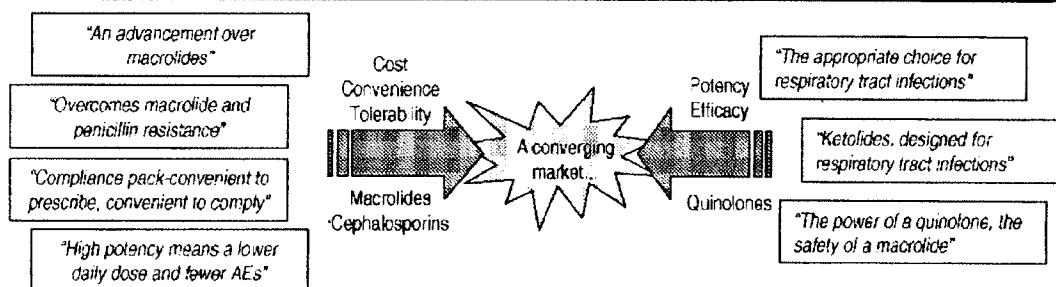
**Steady-state plasma concentrations are well above MIC<sub>90</sub>s of key community respiratory pathogens**



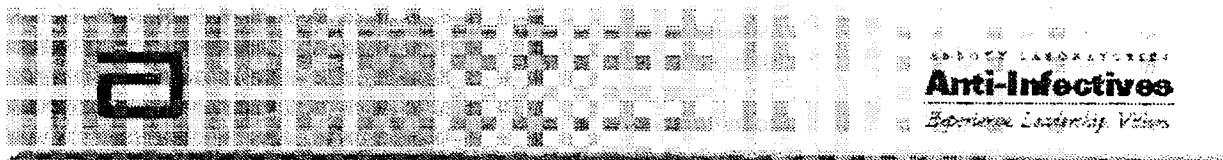
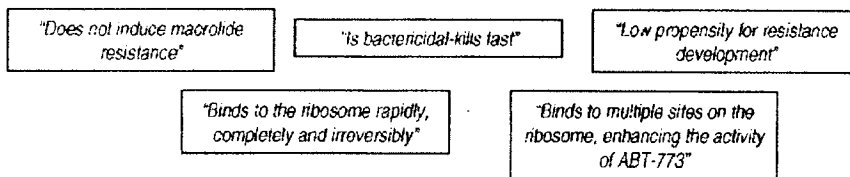
Quinolones are using PK as means of differentiating products—could increase the relevance of PK to prescribers



## Key Commercial Messages



### Supportive Messages

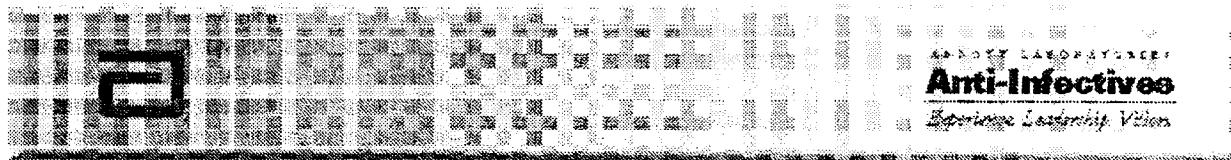




## ***Communications Strategy***

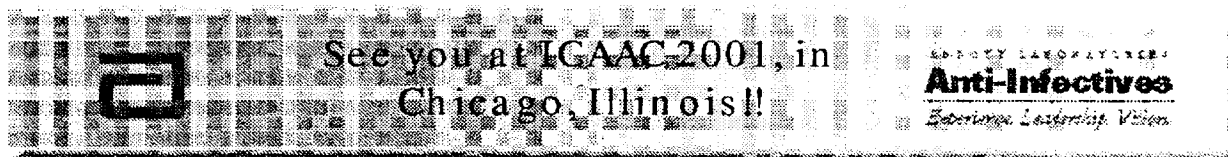
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- Messages
  - microbiological data (resistance, the better ketolide)
  - PK (no food effect, favorable drug-drug)
  - Mechanism (ribosome binding, PAE, etc., "explanation" for ketolide activity, defense of dose selection)
  - Clinical data
- Implementation
  - Strategic initiation of studies to support desired messages, monthly strategy meetings, intranet under development to manage activities/history
  - Scientific meetings (51 posters at 6 scientific meetings in 1999-2000)
  - Publications (10 publications in 2000)
  - Medical Liaisons(sp)
  - VIP Visits



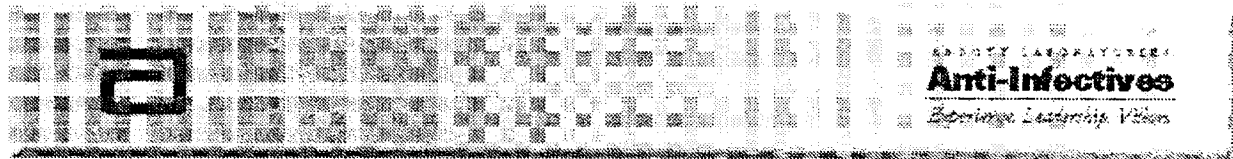
## ICAAC 2000

*International Conference on Antimicrobial Agents and Chemotherapy, Toronto*



**Forecast Assumptions**

	<u>US</u>	<u>Europe</u>	<u>Japan</u>
Dosing	150 mg QD dosing all indications AECB & Phar, 5 d CAP & ABS, 10 d		
Efficacy	Comparable to other agents		
AEs	Comparable to Biaxin XL		
COGS	\$3,000/kg at launch		
AWP/Day	\$8.60		



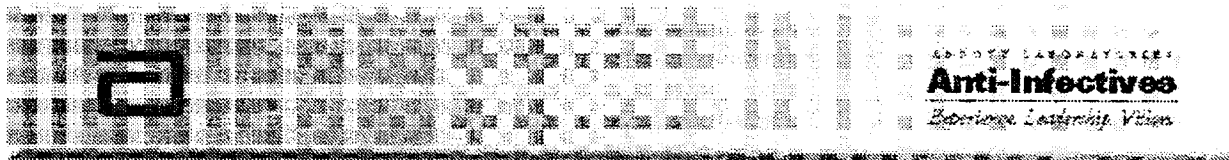
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ABBT205127

**Forecast**

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	<u>U.S.</u>	<u>Europe</u>	<u>Japan</u>	<u>ROW</u>	<u>Total</u>
Peak Sales	\$432MM				
Peak TRX Share	7.5%				N/A
NPV @12.5%					



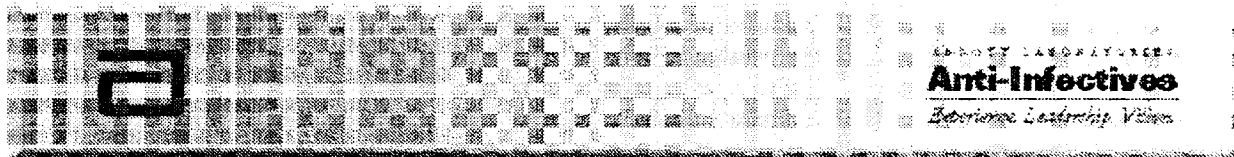
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ABBT205128

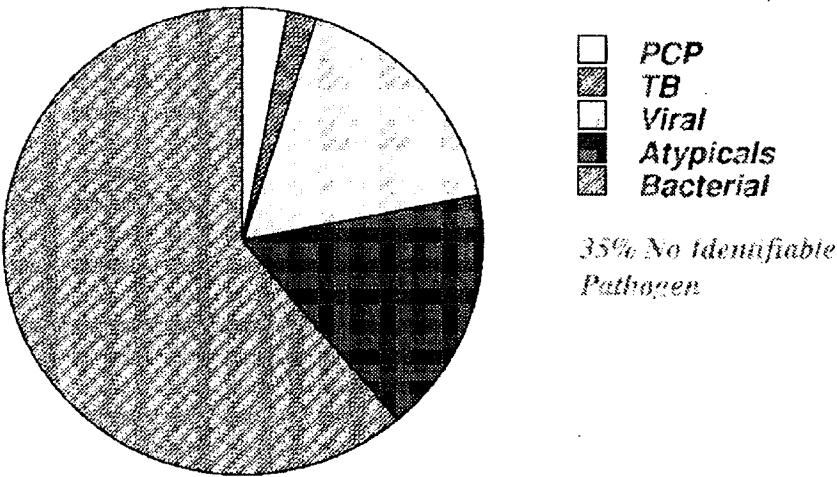
## **Microbiology** *Overview*

---

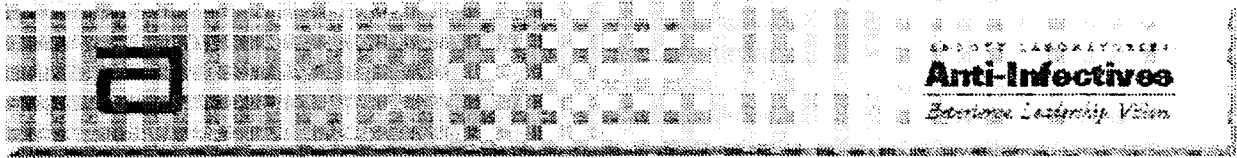
- **Ketolides are a Novel Class of Antimicrobial**
  - Active vs. key respiratory tract infection pathogens to include macrolide resistant streptococci
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development



**Microbiology**  
*Community-Acquired Pneumonia in Adults*

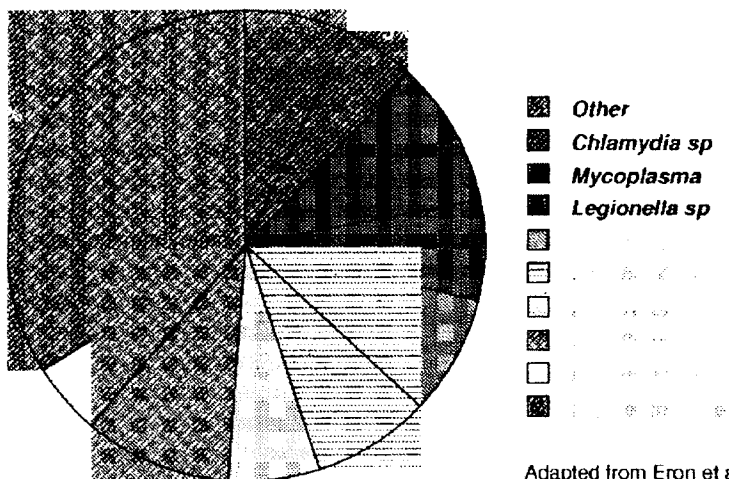


Adapted from Eron et al. Hosp Form 1994;29:122

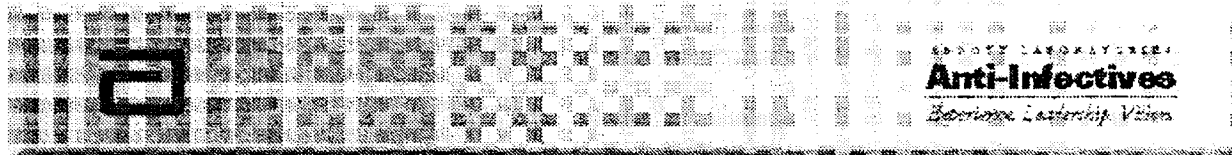


**Microbiology**

### Bacterial Causes of Community-Acquired Pneumonia in Adults

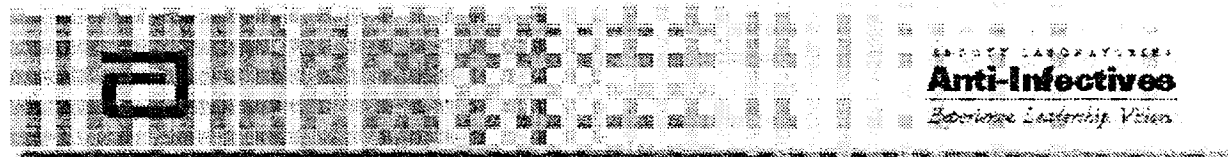
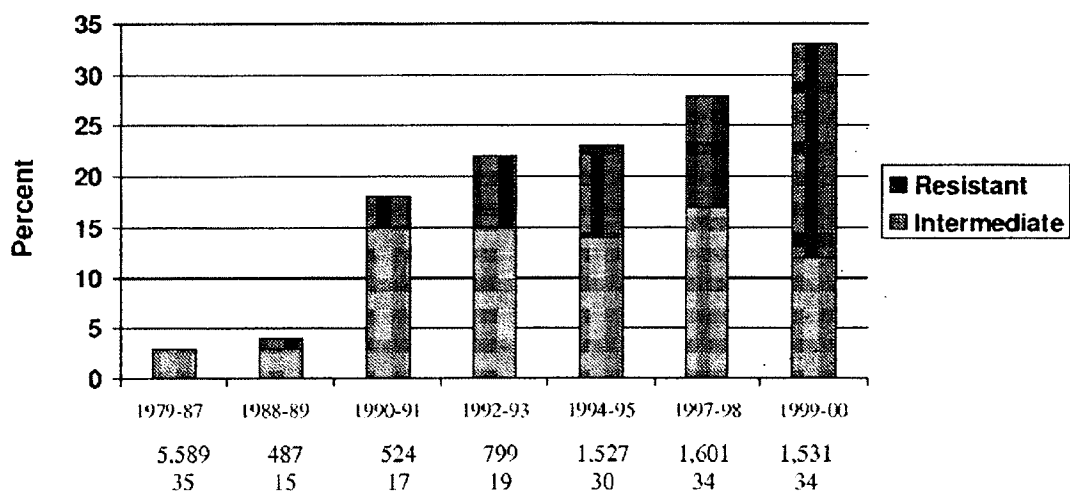


Adapted from Eron et al. Hosp Form 1994;29:122



**Microbiology**

**Penicillin resistance with *Streptococcus pneumoniae* in the United States**



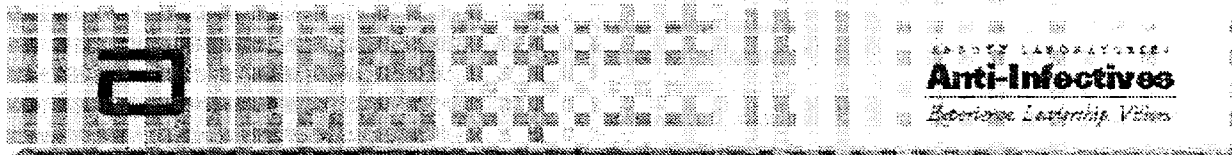


**Microbiology*****US Respiratory Surveillance Studies, Penicillin Susceptibility in *S. pneumoniae****

---

Year	1994-95	1997-98	1999-2000
Season	Winter	Winter	Winter
No. of centers	30	34	34
No. of isolates	1,528	1,601	1531
No. % intermediate	216 (14.1)	278 (17.4)	194(12.7%)
No. % resistant	145 (9.6)	196 (12.2)	29 (21.5%)

Dr. G. Doern, Univ. of Iowa



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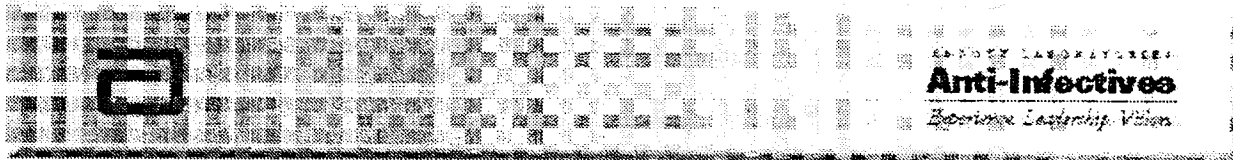
ABBT205133

# PART 6

**Microbiology**  
**Antimicrobial Resistance Rates among *S. pneumoniae***

	1994-95	1997-98	1999-2000
Antimicrobial Agent	N=1527	N=1601	N=1531
Macrolide	10.0	18.9	25.9
Tetracycline	7.5	12.9	16.4
Chloramphenicol	4.3	7.2	8.4
Clindamycin	Na	5.6	8.8
TMP/SMX	18.0	20.4	30.3

Dr. G. Doern, Univ. of Iowa



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ABBT205134

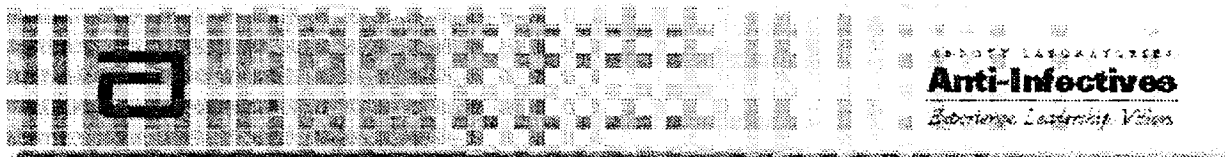
**Microbiology**

*Rates of Resistance of Non-  $\beta$ -Lactam Antimicrobials with Streptococcus pneumoniae  
Based on Penicillin Susceptibility Category*

Percentage Resistance Among

Antimicrobial	PenS-(n=1,008)	PenI(n=194)	PenR(n=1,531)
Macrolides	5.6	43.3	78.1
Clindamycin	1.4	19.1	25.2
Chloramphenicol	1.0	13.9	27.7
Tetracycline	3.1	32.0	48.0
TMP/SMX	7.6	39.2	94.5

[n=1,531, 34 U.S. centers, 1999-2000], Doern et al

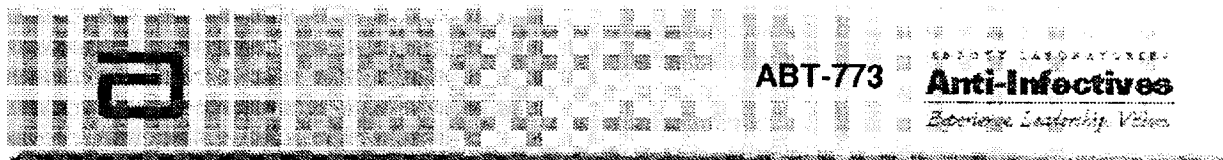
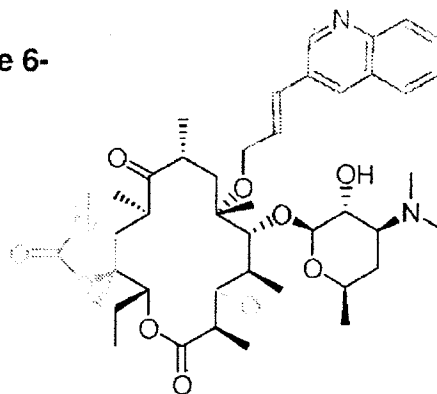


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ABB1205135

**Microbiology**  
**ABT-773 Structure/SAR**

- Quinolylallyl propenyl moiety at the 6-0 -position
- Keto group at the 3-position
- Carbamate group at the 11, 12-position



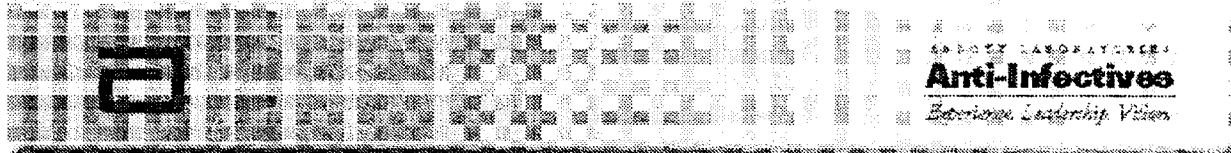
**Microbiology**  
**Macrolide Resistance Types**

---

**Microbiology Overview**

• **Two major macrolide resistance mechanisms in streptococci and staphylococci:**

- Ribosomal methylase – blocks macrolide binding to target
  - Macrolide and clindamycin MIC >16 µg/mL
- Macrolide efflux – actively pumps macrolide out of cell
  - Macrolide MIC 1-32 µg/mL; clindamycin MIC ≤ 0.25 µg/mL



**Microbiology**

**Resistance Mechanisms Prevalence in *S. pneumoniae* Clinical Isolates**

---

Genotype	U.S. 1994-95 <sup>1</sup> n=114	U.S. 1997-98 <sup>2</sup> n=302	Canada <sup>3</sup> n=147	Europe <sup>4</sup> n=21	Japan <sup>5</sup> n=62
<b><i>ermB</i></b>	<b>32%</b>	<b>29%</b>	<b>39%</b>	<b>97%</b>	<b>40%</b>
<b><i>mefE</i></b>	<b>61%</b>	<b>71%</b>	<b>56%</b>	<b>3%</b>	<b>43%</b>
<b><i>mef/erm</i></b>	<b>5%</b>	<b>–</b>	<b>&lt;1%</b>	<b>-</b>	<b>16%</b>
<b>Unknown</b>	<b>2%</b>	<b>–</b>	<b>6%</b>	<b>-</b>	<b>0%</b>

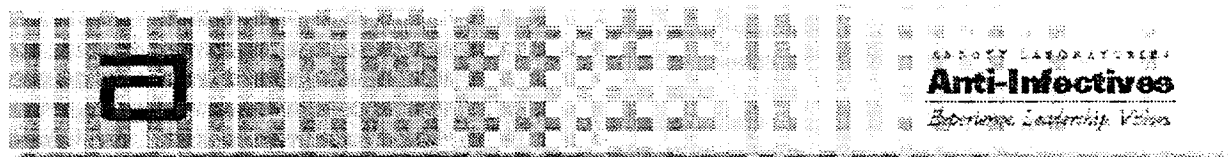
<sup>1</sup>Shortridge, et al. *CID*. 1999; 29:1186-8.

<sup>2</sup>Doern, et al. *EID*. 1999; 5(6).

<sup>3</sup>Johnston, et al. *AAC*. 1998; 42:2425-26.

<sup>4</sup>Schmitz et. al. *JAC*. 1999.43:783-92

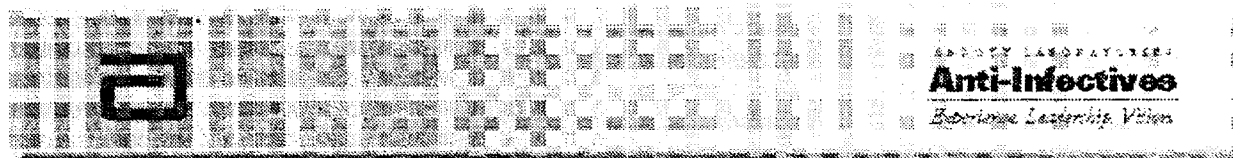
<sup>5</sup>Nishijima et. al. *JAC*. 1999.43:637-643



**Microbiology****ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Erythromycin MIC**

Drug	Erythromycin MIC ≤0.5 µg/ml (n=1299)		Erythromycin MIC 1-32 µg/ml (n=222)		Erythromycin MIC ≥64 µg/ml (n=80)	
	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	≤0.008	≤0.008 - 0.12	0.03	≤0.008 - 0.5	0.12	≤0.008 - 0.5

1997-1998 Survey, Brueggemann et. al.2000. AAC. 44:447-449



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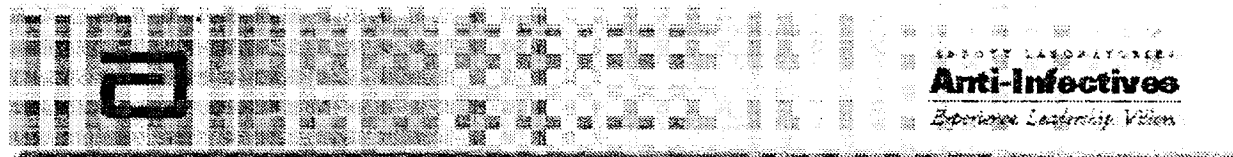
ABB T205139



**Microbiology****ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Penicillin MIC**

	Penicillin Susceptible MIC $\leq 0.06$ $\mu\text{g/ml}$ (n=1127)		Penicillin Intermediate MIC 0.12-1.0 $\mu\text{g/ml}$ (n=278)		Penicillin Resistant MIC $\geq 2.0$ $\mu\text{g/ml}$ (n=196)	
Drug	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	$\leq 0.008$	$\leq 0.008 - 0.5$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.25$
Ery	0.06	$\leq 0.03 - >64$	$>64$	$\leq 0.03 - >64$	$>64$	$\leq 0.03 - >64$

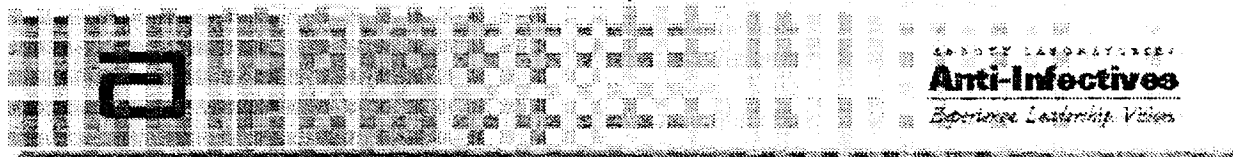
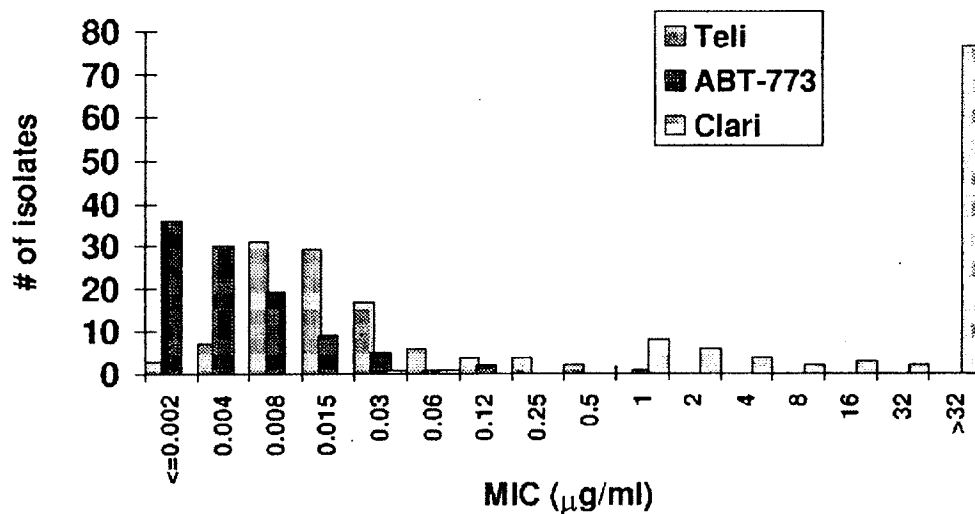
1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449



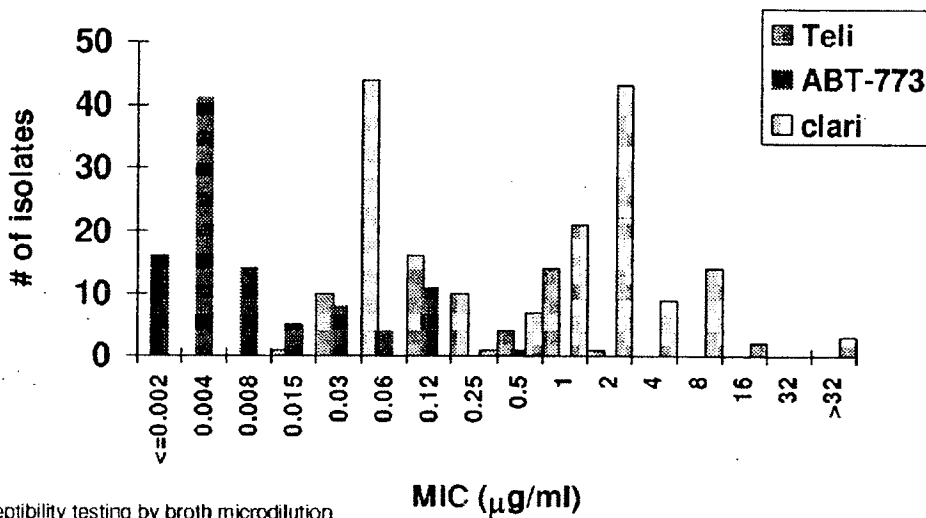
Confidential

ABBT205140

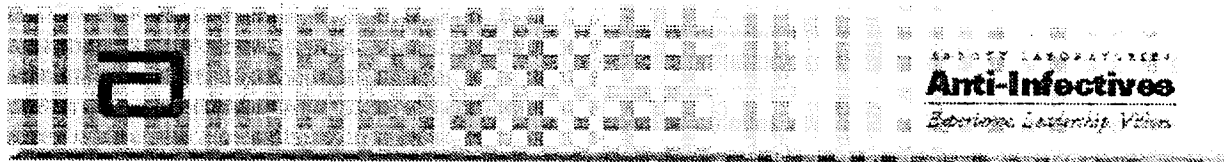
**Microbiology**  
**MIC Distribution of *S. pneumoniae* methylase<sup>+</sup> strains**



**Microbiology**  
*MIC Distribution of S. pneumoniae efflux<sup>+</sup> strains*



Susceptibility testing by broth microdilution



**Microbiology**  
*In vitro Activity, S. pyogenes*

MIC<sub>90</sub> Range in µg/ml

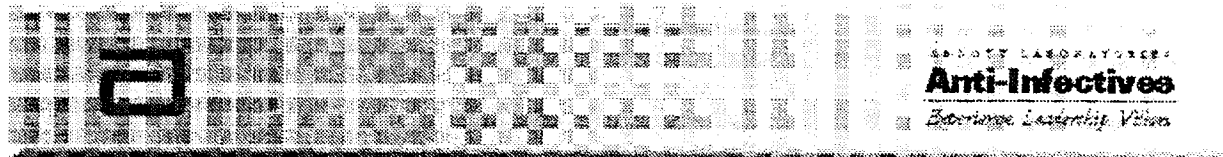
Organism	Macrolide susceptible	Macrolide resistant
ABT-773	≤0.016 - 0.03	0.06 - 0.12
Erythromycin	0.06 - 0.12	8 - 16

References:

Barry et al ICAAC 1999 #2144

Dubois et al. ICMASKO 2000 #2.15

Singh et al. ICMASKO 2000 #2.14



Confidential

ABB205143

**Microbiology***In vitro Activity, Haemophilus, Moraxella spp.***MIC<sub>90</sub> Range in µg/ml**

Organism	<i>H. influenzae</i>	<i>M. catarrhalis</i>
ABT-773	2 - 4	0.06 - 0.25
Azithromycin	2 - 4	0.06 - 0.12
Erythromycin	8 - 16	0.25 - 0.5

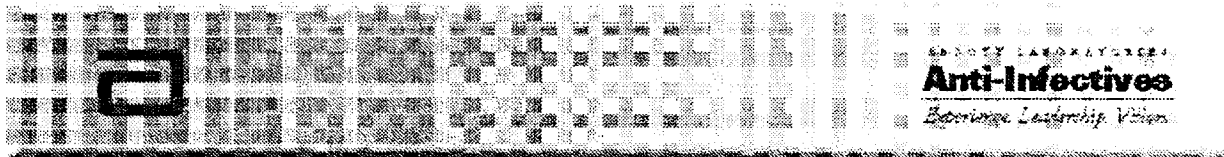
**References:**

Barry et al ICAAC 1999 #2144

Hoellman et al ICAAC 1999 #2140

Brueggemann et al. 2000.AAC.44:447-449

Shortridge et. al.1999. ICAAC



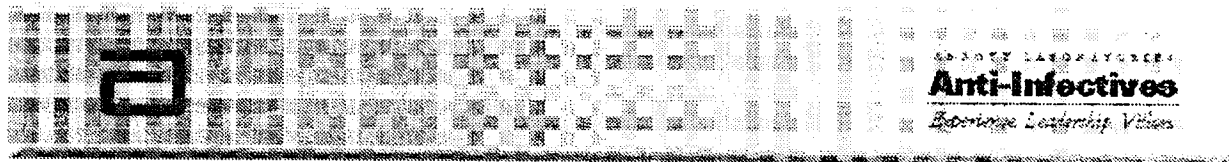
**Microbiology****Comparison of activity vs. respiratory atypical pathogens**MIC<sub>90</sub> in µg/ml

Organism	ABT-773	Ery
<i>Legionella</i> spp. <sup>1</sup> (105)	0.03-0.12	0.25-1.0
<i>M. pneumoniae</i> <sup>2</sup> (18)	≤ 0.0005	0.008
<i>C. pneumoniae</i> <sup>3</sup> (20)	0.015	0.06

<sup>1</sup>Victor Yu, ICAAC, 2000. Strains tested: *L. pneumophila* serogroup 1 (68), *L. pneumophila* other serogroups (28), *Legionella* spp other than pneumophila (10).

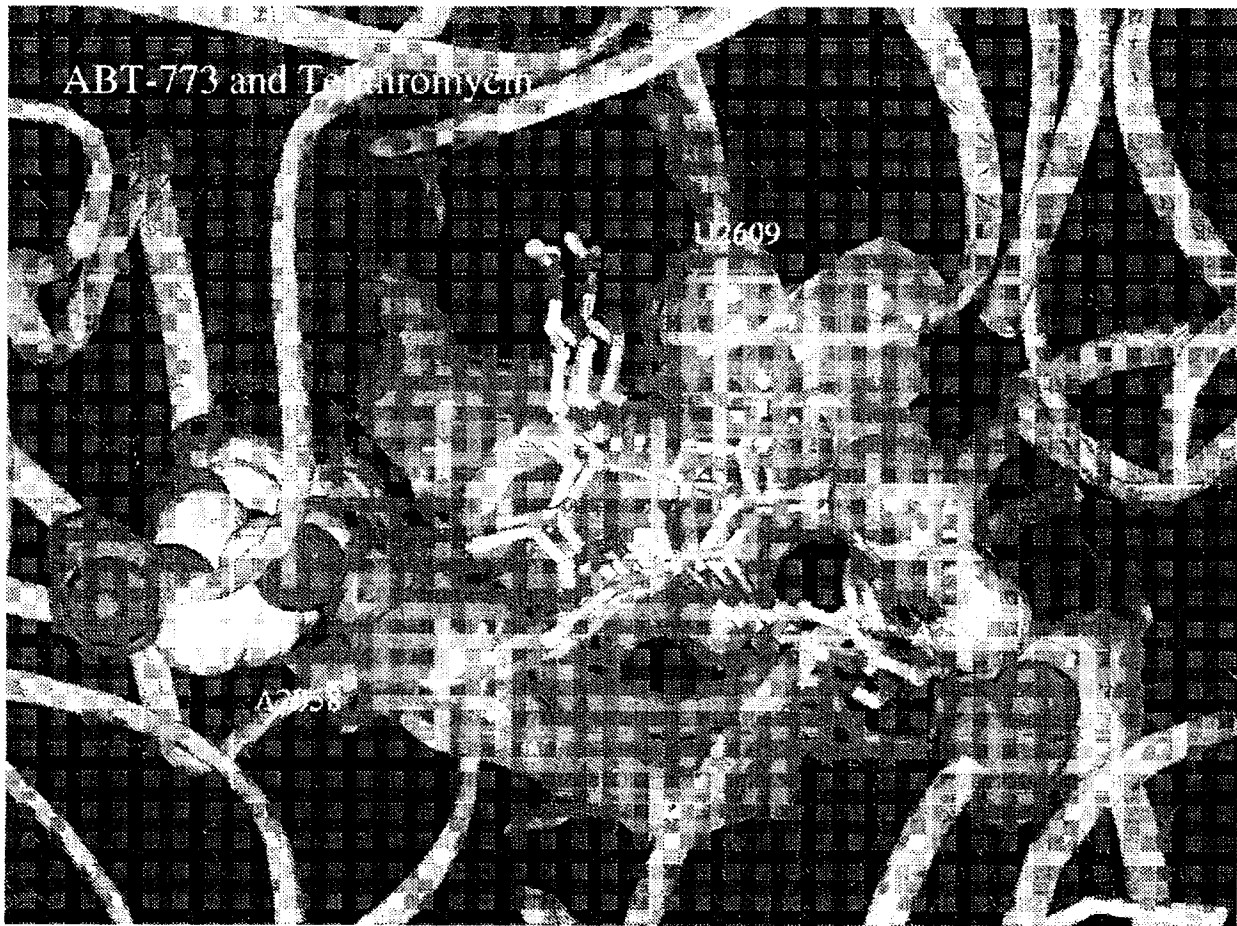
<sup>2</sup>Nilius et al. ECCMID 1999.

<sup>3</sup>Strigl et. al.2000. AAC 44:1112-1113



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ABBT205145



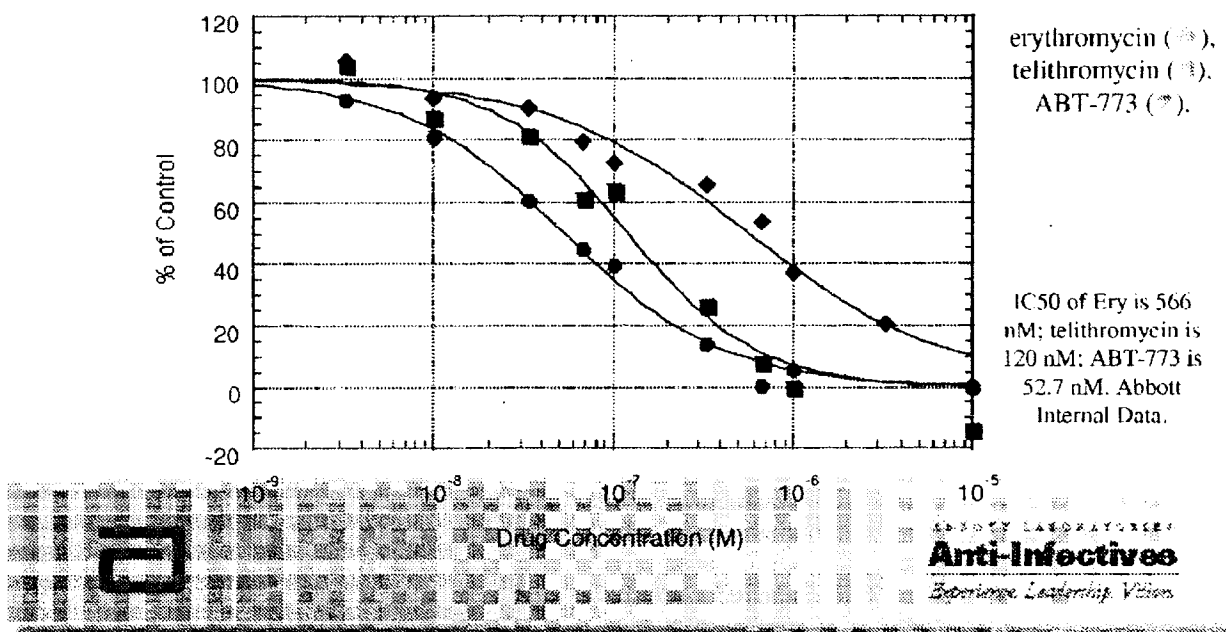
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ABBT205146



## Microbiology

Ribosome Binding, Susceptible *S. pneumoniae*

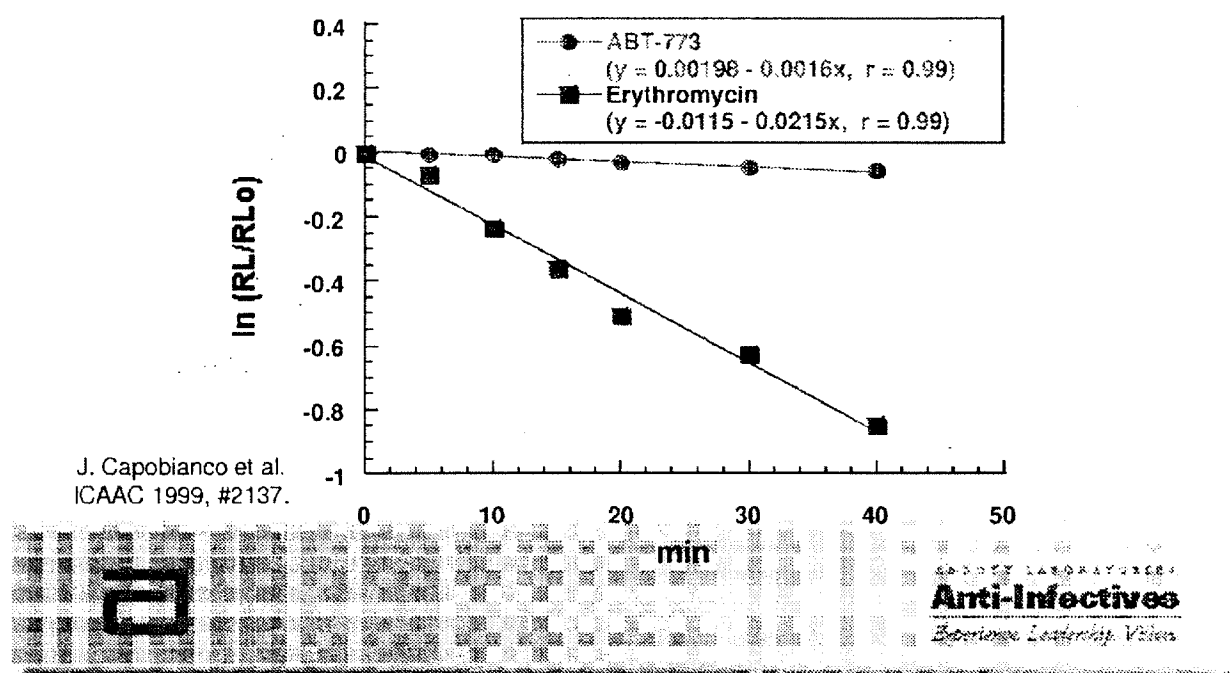


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ABB205147



## ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



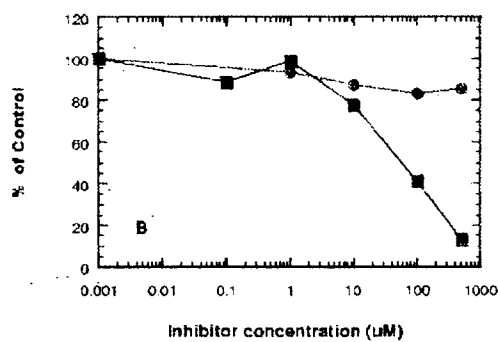
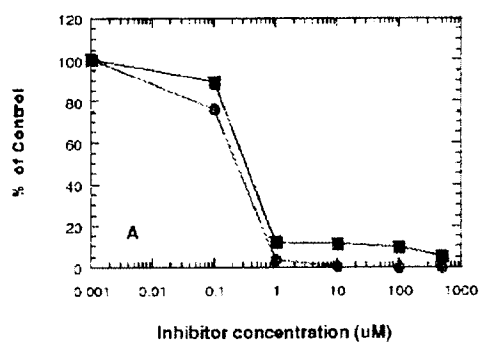
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ABBT05148

**Microbiology**  
Inhibition of Transcription / Translation

S30 from susceptible *S. pneumoniae*

S30 from resistant *S. pneumoniae*

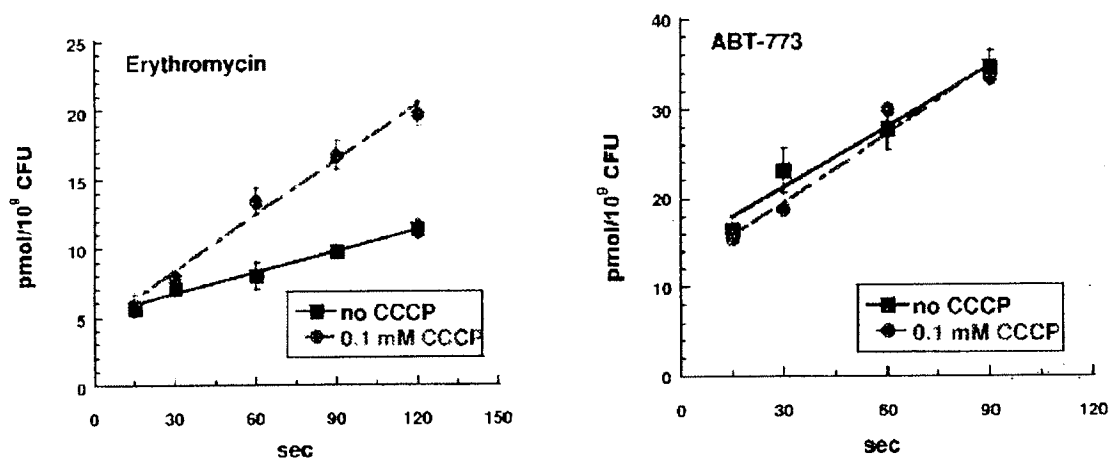


Red circles: erythromycin  
Blue squares: ABT-773

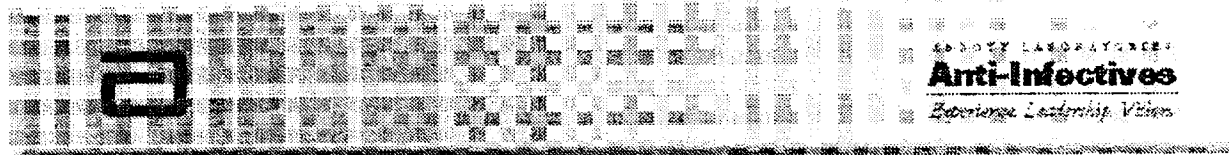


## Microbiology

**ABT-773 Accumulation in efflux<sup>+</sup> strain, with and without pump inhibitor (CCCP)**

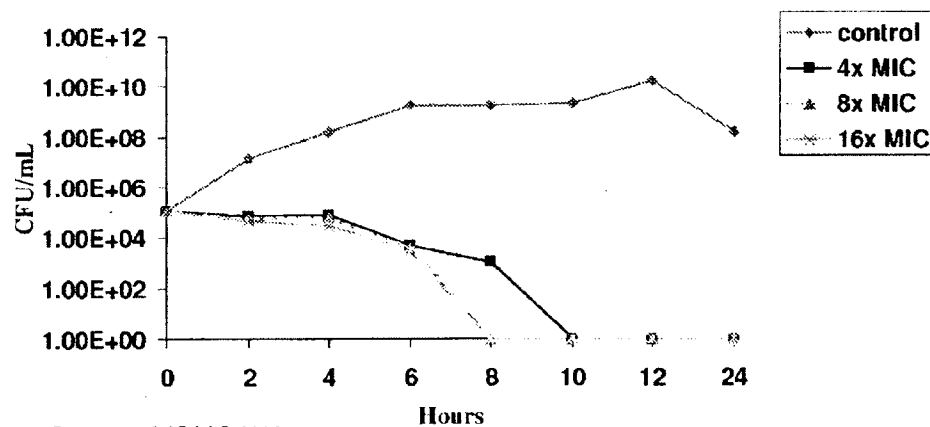


J. Capobianco et al. ICAAC 1999, #2137

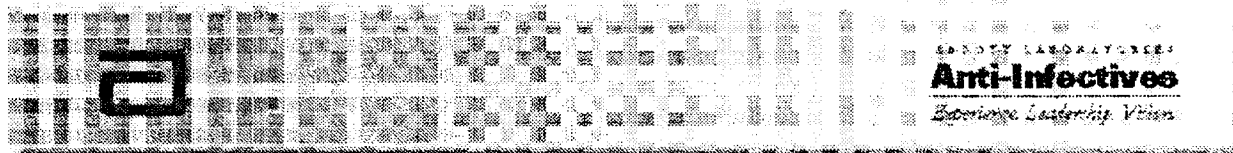


**Microbiology**  
*Bactericidal Activity, S. pneumoniae*

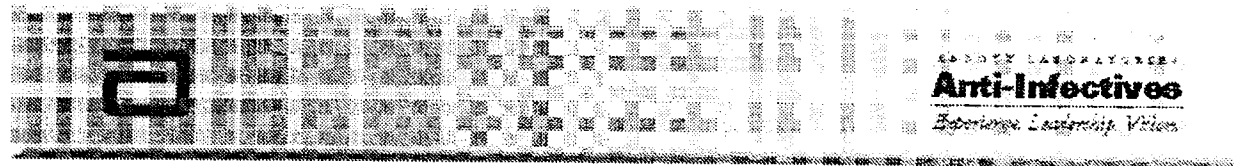
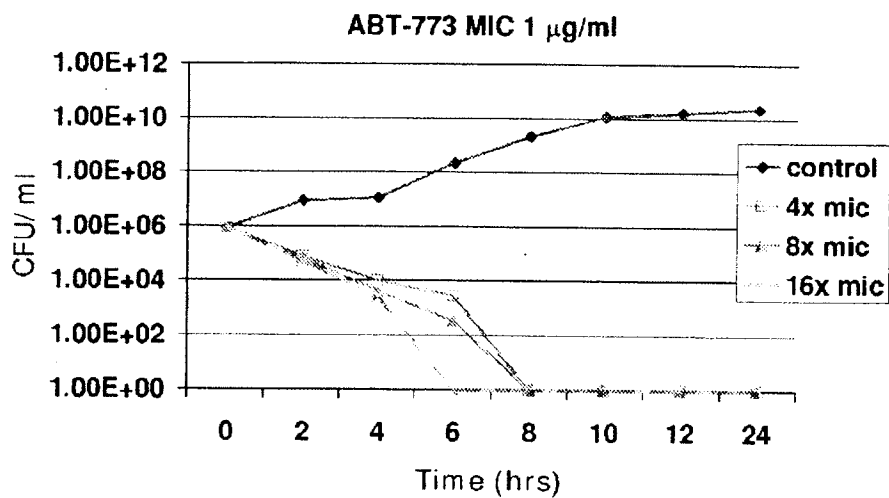
Susceptible *S. pneumoniae*; ABT-773 MIC 0.002 µg/ml



Ramer et al. ICAAC 2000



**Microbiology**  
*Bactericidal Activity, H. influenzae*



Confidential

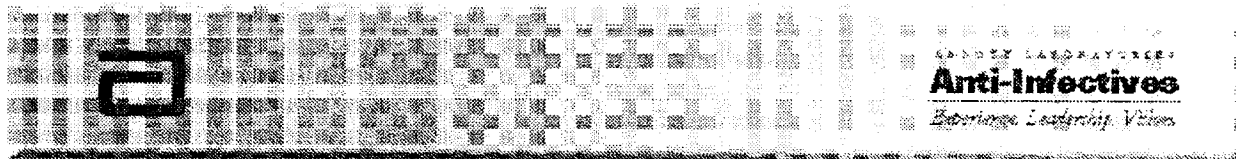
ABBT205152

### **Microbiology**

**Post Antibiotic Effect**

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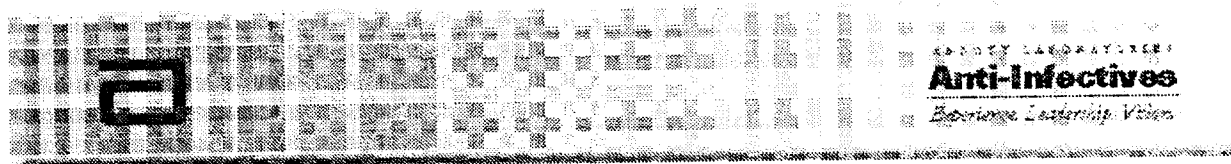
- After removal of drug the bacterial growth rate is inhibited
- Justification for dosing regimen such as QD vs. BID
- Addresses resistance development issues
- In vitro
  - *S. pneumoniae*
    - 8 strains
    - mean PAE ABT-773  $\geq 6.1$  hr
    - mean PAE ery 3.8hr
  - *H. influenzae*
    - 5 strains
    - mean PAE ABT-773  $\geq 6.1$  hr
    - mean ery PAE 3.8 hr



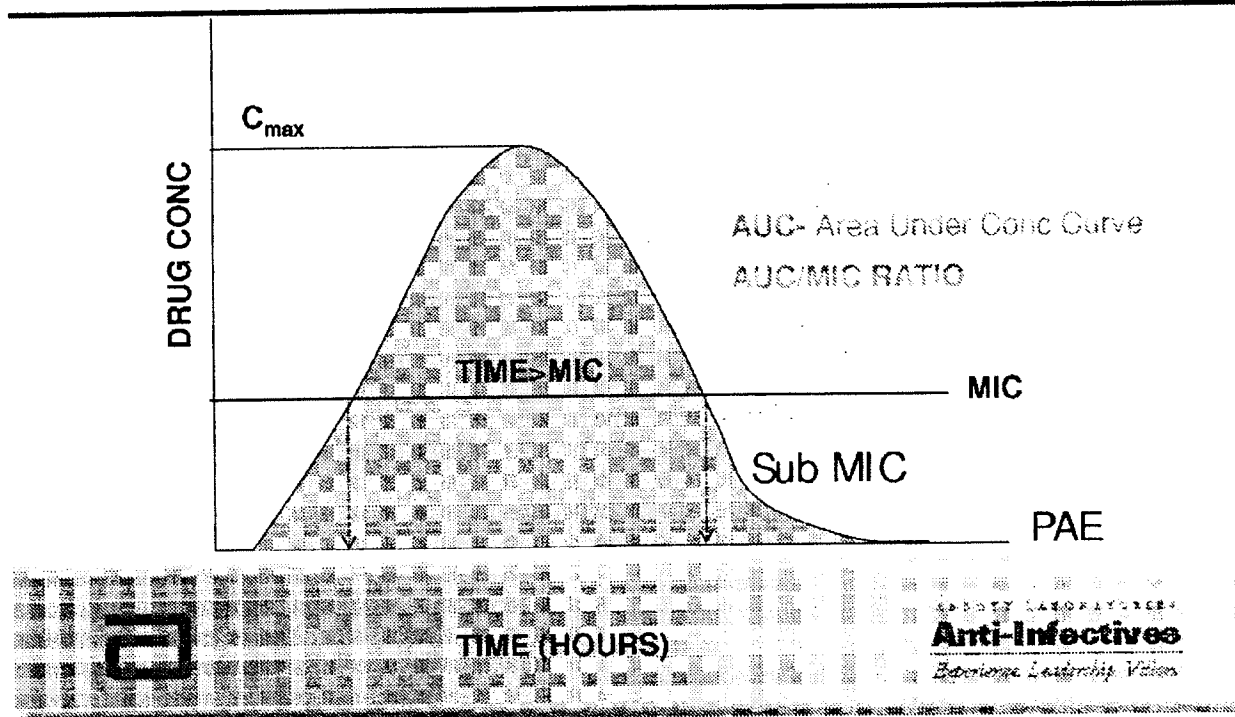
**Microbiology**  
**Resistance Development**

---

- **Occur by mutation**
  - Quinolone resistance in GyrA and ParC
- **Acquired from another bacterium**
  - Methylase
  - Efflux
- ***S. pneumoniae***
  - In vitro single step mutation frequency (8XMIC)
    - 1 *S. pneumoniae* (S)  $<5.6 \times 10^{-10}$
    - 1 *S. pneumoniae* *mef*  $<2.6 \times 10^{-12}$
    - 2 *S. pneumoniae* *ermB*  $3.5 \times 10^{-10}$  -  $<9.4 \times 10^{-11}$
  - Mutation frequency for rifampicin (8XMIC)
    - 4 *S. pneumoniae*  $1.2 \times 10^{-6}$  to  $3.0 \times 10^{-7}$
  - No difference in mutation rate if macrolide resistant or susceptible
  - Low potential for resistance development



**Microbiology**  
**Pharmacodynamic Parameters**



Confidential

ABB T205155

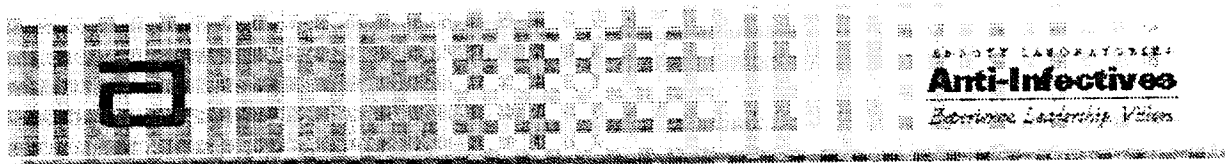


**Microbiology**  
*In vivo pharmacodynamics*

---

• **Antibiotic exposure needed for efficacy against *S. pneumoniae* in animal models**

- AUC/MIC is best predictive parameter for ketolides
- Rat lung model of pneumonia with *S. pneumoniae*
  - QD an AUC 0-24 ug.h/ml of 0.4-1.0 for an MIC<sub>90</sub> of 0.12
  - BID an AUC 0-24 ug.h/ml of 0.1-0.4 for an MIC<sub>90</sub> of 0.12
- Lethal mouse model of pneumonia AUC 0-24 of <3-6 ug.h/ml



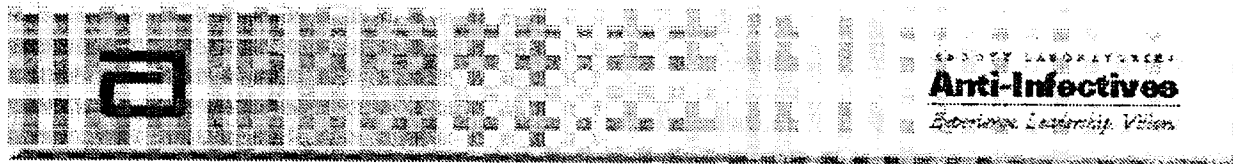
**Microbiology**  
*In vivo pharmacodynamics*

---

- **Neutropenic mouse thigh model**

- *S. pneumoniae*
  - 6 macrolide susceptible , 8 macrolide resistant
  - $10^{5.6-7.4}$  CFU/ thigh
  - ABT-773 dose 0.023-24 mg/kg/day Q6 h
  - Net bacteriostatic effect over 24 hrs is measured

Andes, D.R. and W.A. Craig. ICAAC 2000.



Confidential

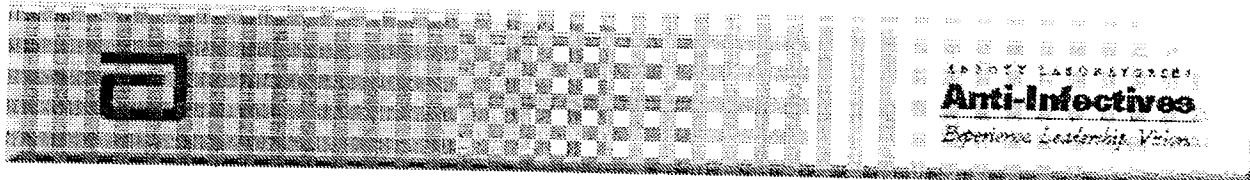
ABBT05157

**Microbiology**  
*In vivo pharmacodynamics*

---

- **Neutropenic mouse thigh model- *S. pneumoniae***
  - 24hr AUC/MIC is best PK/PD predictor
  - Prolonged PAEs with concentration dependent killing
    - up to 11 hrs
  - Magnitude of AUC/MIC is not significantly altered by macrolide resistance with strains with MICs as high as 0.5µg/ml

Andes, D.R. and W.A. Craig. ICAAC 2000



Confidential

ABBT205158

## **Microbiology**

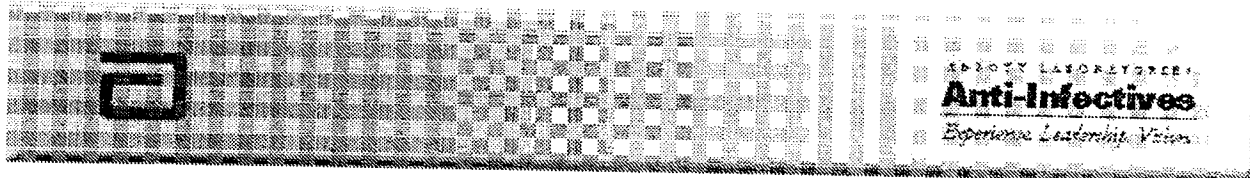
*In vivo pharmacodynamics*

---

- **Mouse lethal pneumonia model**

- *S. pneumoniae*-2 strains
  - eryS
  - eryR
- immunocompetent mice
- infected with  $10^{4-5}$  CFU
- treatment 6 or 12 hr post-infection
- subcutaneous dosing
- BID treatment for 3 days

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. IGAAC 2000.



Confidential

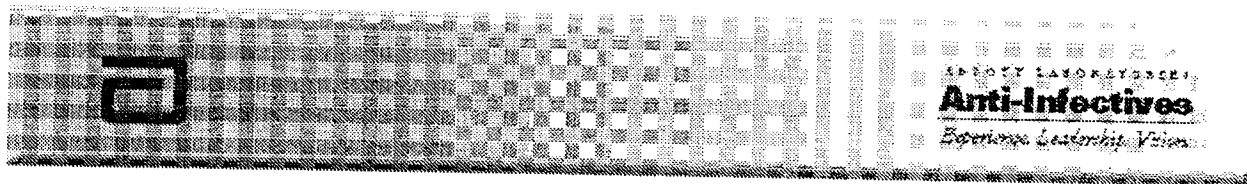
ABBT205159

**Microbiology**  
*In vivo pharmacodynamics*

---

- **vs. macrolide susceptible**
  - Ery/ABT-773 MIC 0.015/0.015 ug/ml
    - 100% survival with 3 days of treatment at s.c. 6.25mg/kg
- **vs. macrolide resistant**
  - Ery/ABT-773 MIC 1024/0.03 ug/ml
    - 93% survival with 3 days of treatment s.c. at 12.5 mg/kg
      - » infected mouse single dose 12.5 mg/kg- AUC 0-24 ug.h/ml 3.08+/- 0.32)

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAG 2000.



Confidential

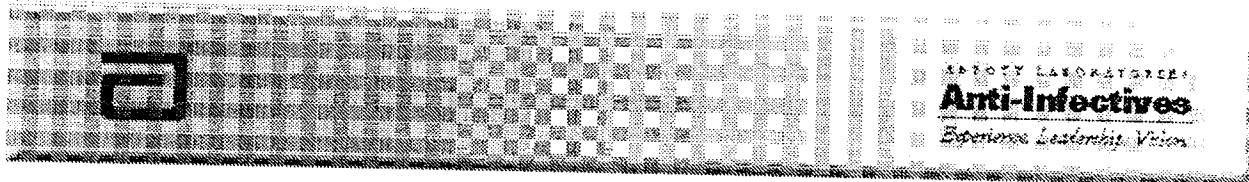
ABBT205160

**Microbiology**  
*In vivo pharmacodynamics*

---

- Suggests total daily AUC 0-24 ug.h/ml of  $<3-6$  is sufficient for pneumonia
  - ketolide is active vs macrolide resistant strain unlike erythromycin
  - no resistant mutants emerged vs ABT-773 but did for erythromycin

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.



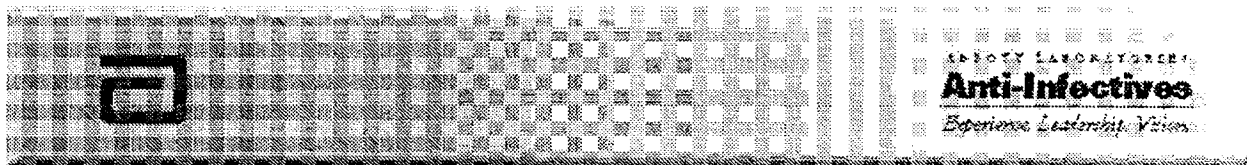
Confidential

ABBT205161

**Microbiology**  
**Summary**

---

- Active vs. key respiratory pathogens including macrolide resistant streptococci
- Bactericidal
- Extended PAE
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome
  - Exposure of  $<1 \text{ ug.h/ml AUC}_{24}$  for mild to moderate pneumonia model and  $\text{AUC}_{24} \text{ ug.h/ml} <3-6$  for more severe model

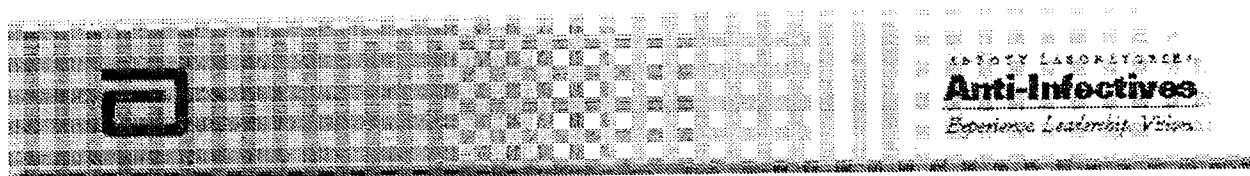


# PART 7



***Phase II Clinicals***  
*Joaquin Valdes*

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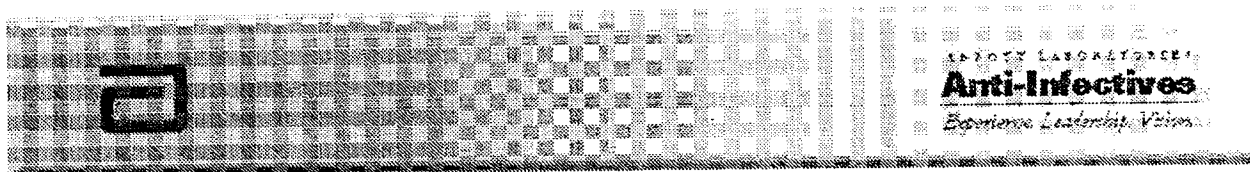


Confidential

ABBT205163

**Phase II Clinicals**  
Program Summary

Study	Study Drug Dose/Duration	Patient Numbers/location
M99-048 Phase IIb, Double blind Acute Bacterial Exacerbation of Chronic Bronchitis	ABT-773 150, 300 or 600 mg OD Duration: 5 days	N = 384 US, Germany, France, Italy, Spain, UK, Chile
M99-053 Phase IIb, Double-blind Acute Sinusitis	ABT-773 150, 300, or 600 mg OD Duration: 10 days	N = 292 US, Finland, Greece, Chile
M99-054 Phase IIb, Double-blind Community Acquired Pneumonia	ABT-773 300 or 600 mg OD Duration: 7 days	N = 187 US, Germany, France, Italy, Spain, Poland, South Africa



Confidential

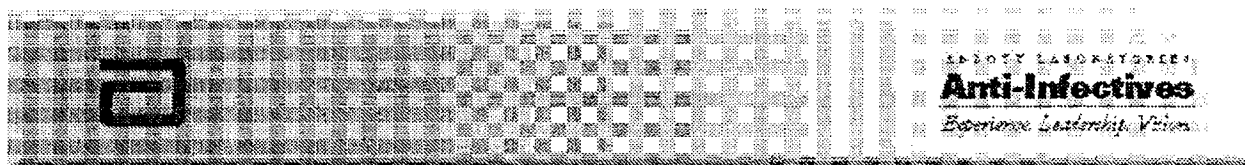
ABBT205164

**Acute Bacterial Exacerbation of Chronic Bronchitis**  
**M99-048**  
**Clinical Response**

---

	150 mg		300 mg		600 mg	
Clin and Bact. Eval	84%	(42/50)	88%	(49/56)	94%	(59/63)
Clin Eval	87%	(98/113)	90%	(105/117)	90%	(101/112)
ITT	85%	(104/123)	83%	(107/129)	83%	(106/128)

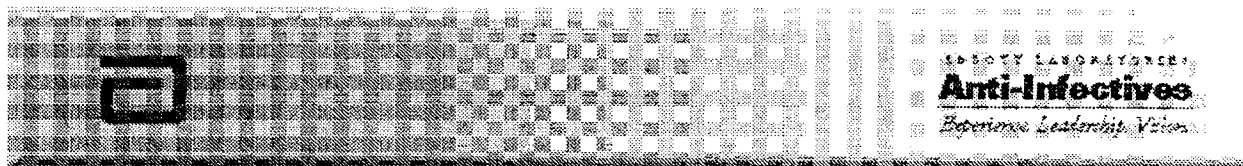
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**Acute Bacterial Exacerbation of Chronic Bronchitis**  
**M99-048**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

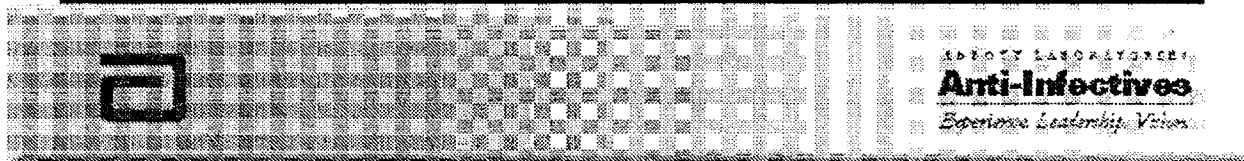
	150mg	300mg	600mg
<i>S. pneumoniae</i>	83% (10/12)	90% (9/10)	100% (13/13)
<i>M. catarrhalis</i>	80% (8/10)	92% (12/13)	91% (10/11)
<i>H. influenzae</i>	94% (17/18)	89% (17/19)	83% (19/23)
Overall	88% (35/40)	91% (38/42)	89% (42/47)



**Acute Bacterial Exacerbations of Chronic Bronchitis**  
**M99-048**  
**Adverse Events**

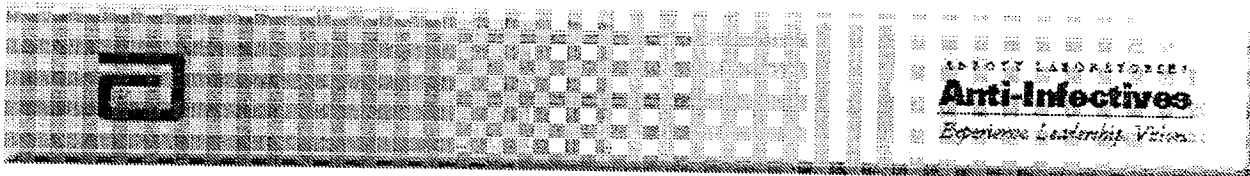
**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
Taste Perversion	6% (7/126)	19% (25/129)	29% (37/129)
Diarrhea	13% (16/126)	12% (15/129)	21% (27/129)
Nausea	7% (9/126)	13% (17/129)	30% (38/129)
Vomiting	2% (3/126)	3% (4/129)	11% (14/129)
Nausea and Vomiting	0	<1% (1/129)	4% (5/129)
Abdominal Pain	4% (5/126)	4% (5/129)	4% (5/129)



**Community-Acquired Pneumonia**  
**M99-054**  
**Clinical Response**

	300 mg	600 mg
Clin and Bact. Eval	92% (54/59)	82% (47/57)
Clin Eval	92% (72/78)	80% (56/70)
ITT	84% (80/95)	73% (65/89)



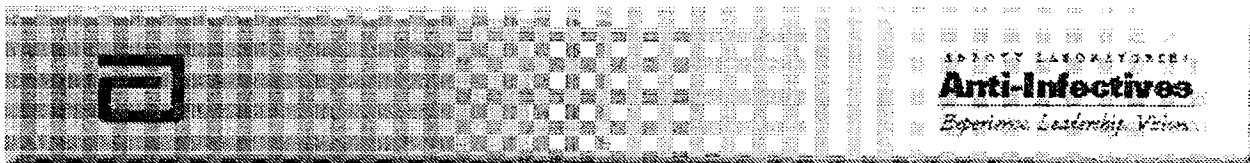
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ABBT205168

**Community-Acquired Pneumonia**  
**M99-054**  
**Radiographic Response**

**(Resolution/Improvement)**

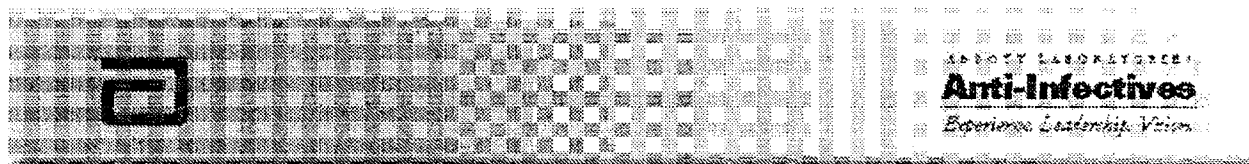
	300 mg	600 mg
Clin and Bact. Eval	100% (56/56)	89% (48/54)
Clin Eval	99% (73/74)	88% (57/65)
ITT	84% (80/95)	72% (64/89)



**Community-Acquired Pneumonia  
M99-054  
Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	300 mg		600 mg	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)
<i>M. catarrhalis</i>	75%	(6/8)	50%	(2/4)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)
<i>C. pneumoniae</i>	95%	(19/20)	79%	(19/24)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)
Overall	91%	(63/69)	81%	(57/70)

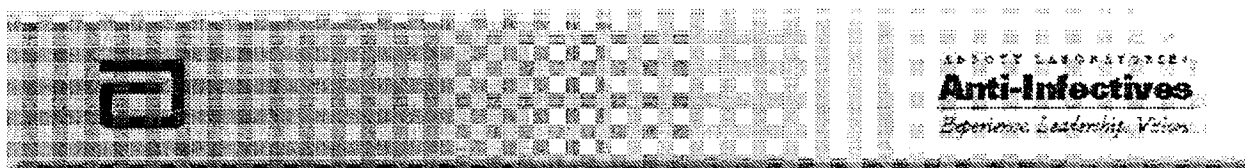




**Community-Acquired Pneumonia**  
**M99-054**  
**Adverse Events**

**All Adverse Events**

	300mg		600mg	
GI and Taste				
Taste Perversion	17%	(16/95)	26%	(24/92)
Diarrhea	14%	(13/95)	19%	(17/92)
Nausea	12%	(11/95)	22%	(20/92)
Vomiting	10%	(9/95)	15%	(14/92)

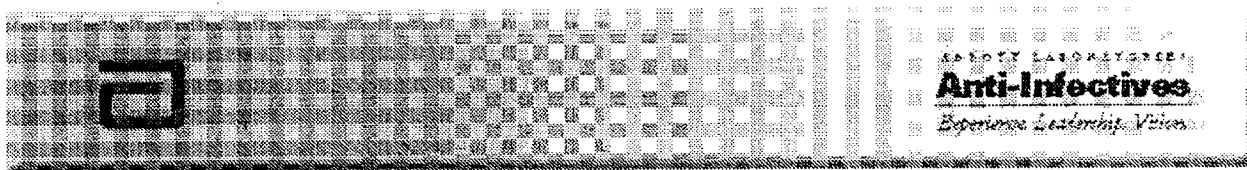


**Sinusitis**  
**M99-053**  
**Clinical Response**

---

	150 mg	300 mg	600 mg
Clin Eval	89% (70/79)	83% (70/84)	71% (59/83)
ITT	82% (72/88)	80% (72/90)	67% (59/88)

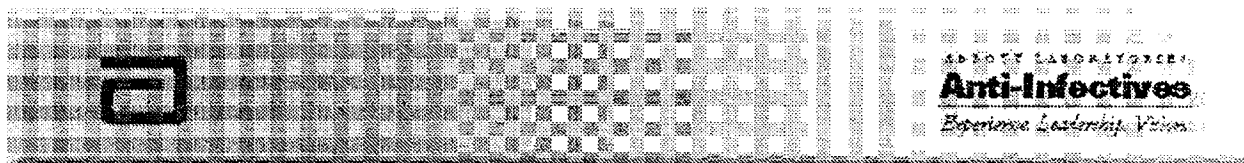
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**Sinusitis  
M99-053  
Radiographic Response**

**(Resolution/Improvement)**

	150 mg	300 mg	600 mg
Clin Eval	86% (68/79)	86% (71/83)	78% (59/76)
ITT	81% (71/88)	81% (73/90)	67% (59/88)

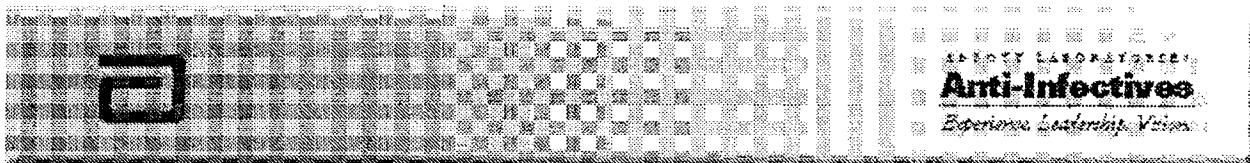


**Sinusitis**  
**M99-053**  
**Bacteriological Response**

---

**Clinically and Bacteriologically Evaluable**

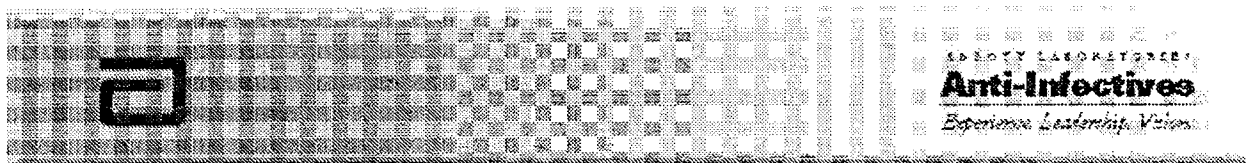
	150mg	300mg	600mg
<i>S. pneumoniae</i>	3/3	8/8	9/12
<i>M. catarrhalis</i>	8/9	3/4	4/4
<i>H. influenzae</i>	3/5	7/7	5/7
<i>S. aureus</i>	1/1	1/1	3/4



**Sinusitis**  
**M99-053**  
**Adverse Events**

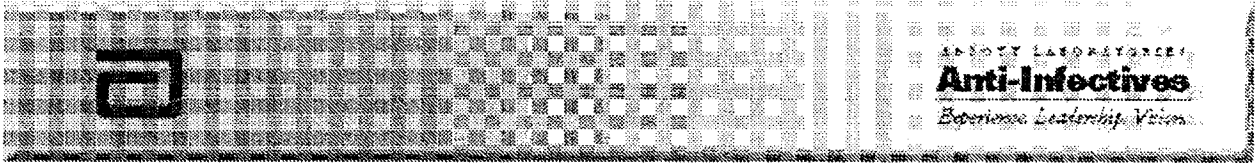
**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
Taste Perversion	1% (1/97)	14% (14/98)	27% (26/97)
Diarrhea	6% (6/97)	6% (6/98)	17% (16/97)
Nausea	3% (3/97)	12% (12/98)	26% (25/97)
Vomiting	1% (1/97)	6% (6/98)	17% (16/97)



*Insert cure/erad/AE summary table*

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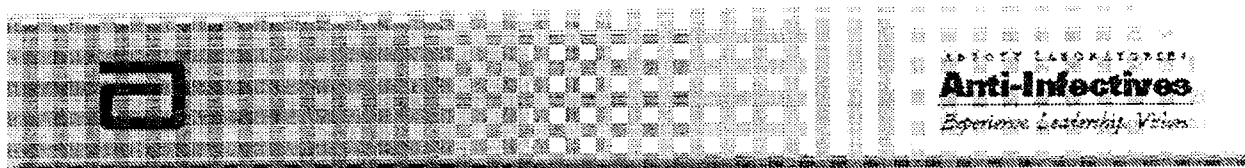


**ABECB, CAP, AMS**  
**M99-048, M99-054, M99-053**  
**Clinical Response**

---

	150 mg	300 mg	600 mg
<b>Clin and Bact. Eval</b>	<b>84%</b> (42/50)	<b>90%</b> (103/115)	<b>88%</b> (106/120)
<b>Clin Eval</b>	<b>88%</b> (168/193)	<b>88%</b> (247/279)	<b>81%</b> (216/265)
<b>ITT</b>	<b>83%</b> (176/211)	<b>82%</b> (259/314)	<b>75%</b> (230/305)

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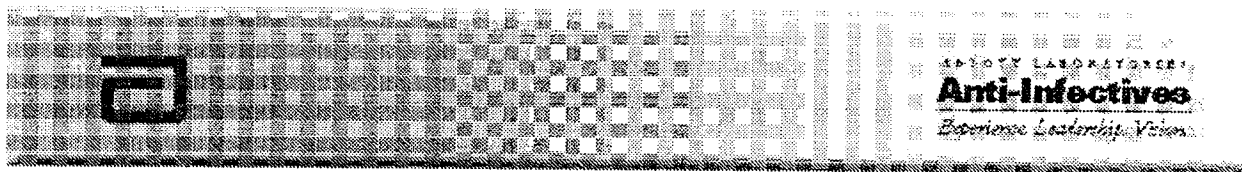
# PART 8



**ABECB, CAP, AMS**  
**M99-048, M99-054, M99-053**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

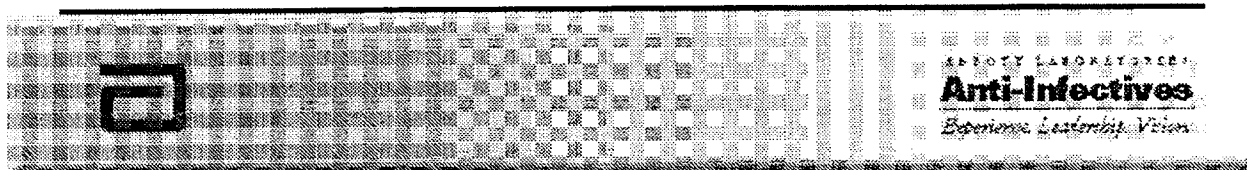
	150mg	300mg	600mg
<i>S. pneumoniae</i>	87% (13/15)	91% (30/33)	91% (29/32)
<i>M. catarrhalis</i>	84% (16/19)	84% (21/25)	84% (16/19)
<i>H. influenzae</i>	87% (20/23)	94% (33/35)	77% (37/48)
Overall	86% (49/57)	90% (84/93)	83% (82/99)



**ABECB, CAP, AMS**  
**M99-048, M99-054, M99-053**  
**Adverse Events**

**All Adverse Events**

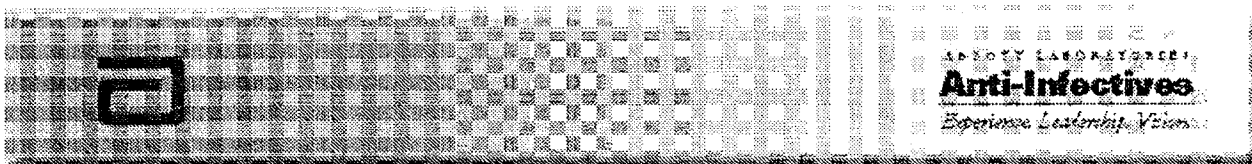
	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
<b>Taste Perversion</b>	<b>4%</b> (8/223)	<b>17%</b> (55/322)	<b>27%</b> (87/318)
<b>Diarrhea</b>	<b>10%</b> (22/223)	<b>11%</b> (34/322)	<b>19%</b> (60/318)
<b>Nausea</b>	<b>5%</b> (12/223)	<b>12%</b> (40/322)	<b>26%</b> (83/318)
<b>Vomiting</b>	<b>2%</b> (4/223)	<b>6%</b> (19/322)	<b>14%</b> (44/318)



### *Phase II summary*

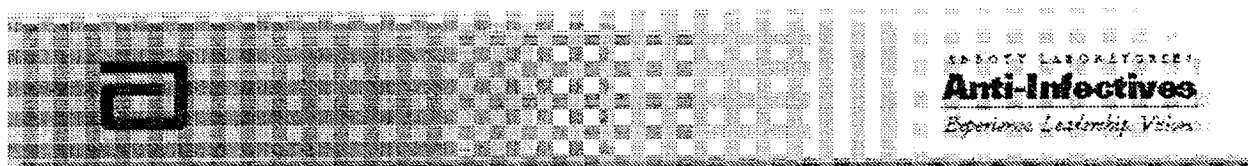
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- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD will be evaluated in comparative studies of ABECB and pharyngitis in phase III
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS



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***Phase III Clinical Program  
Joaquin Valdes***



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ABBT205181

### Proposed Indications and Treatment Duration

Infection	Dosage (QD)	Duration (days)
Pharyngitis/Tonsillitis due to <i>S. pyogenes</i> *	150 mg	5
Acute bacterial sinusitis due to		
<i>H. influenzae</i>	150 mg (or BID)	10
<i>M. catarrhalis</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10
Acute bacterial exacerbation of chronic bronchitis due to		
<i>H. influenzae</i>	150 mg	5
<i>H. parainfluenzae</i>	150 mg	5
<i>M. catarrhalis</i>	150 mg	5
<i>S. pneumoniae</i> **	150 mg	5
Community-acquired pneumonia due to		
<i>C. pneumoniae</i>	150 mg (or BID)	10
<i>H. influenzae</i>	150 mg (or BID)	10
<i>L. pneumophila</i>	150 mg (or BID)	10
<i>M. pneumoniae</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10

\*Including macrolide-resistant strains.

\*\*Including penicillin-resistant and macrolide-resistant strains.

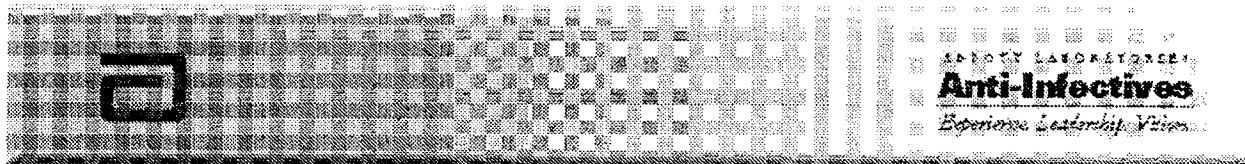
Abbott Laboratories

**Anti-Infectives**

Experience. Leadership. Vision.

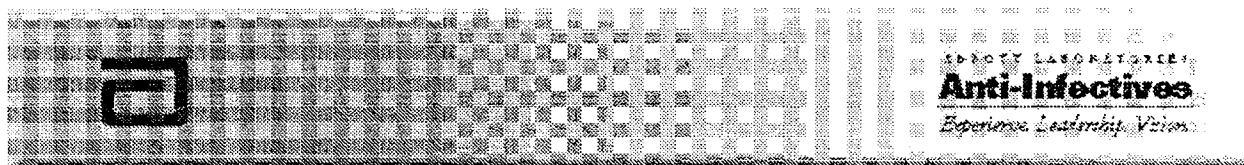
**Phase 3 Studies****Studies starting in year 2000:**

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	260	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	260	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	300	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	250	EU (Non-IND)



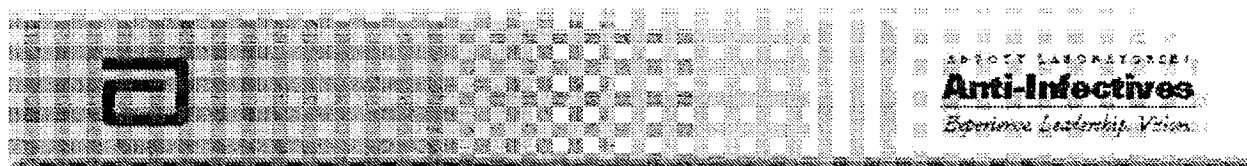
**Phase 3 Studies****Studies starting in year 2000 (Cont.):**

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	600	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	800	US, Canada, EU (IND)



**Phase 3 Studies****Studies starting in year 2001:**

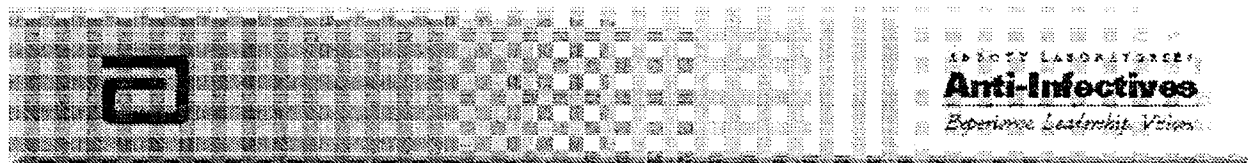
Study	Indication	Comparator	Number ABT-773 Subjects	Location
M00-221	CAP	Levofloxacin	225	US, Canada (IND)
M00-220	CAP	Augmentin or Amoxicillin	250	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	US, Canada (IND)
M00-218	Sinusitis	Augmentin or Quinolone	250	EU (Non-IND)





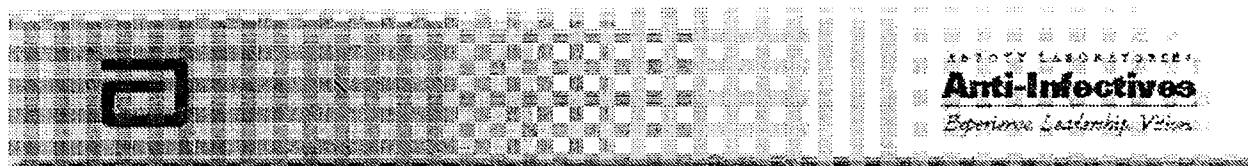
### Proposed Claim for Macrolide or Penicillin Resistant Bacteria and Atypicals

Claim	Supporting Data
Macrolide-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Penicillin-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Macrolide-resistant <i>S. pyogenes</i>	15 isolates worldwide from Phase 3 pharyngitis
Atypicals; <i>C. pneumoniae</i> , <i>M. pneumoniae</i> , <i>Legionella spp.</i>	15 isolates worldwide per organism (include positive serology) from Phase 3 CAP



***Bulk Drug Manufacturing***  
*Ashok Bhatia*

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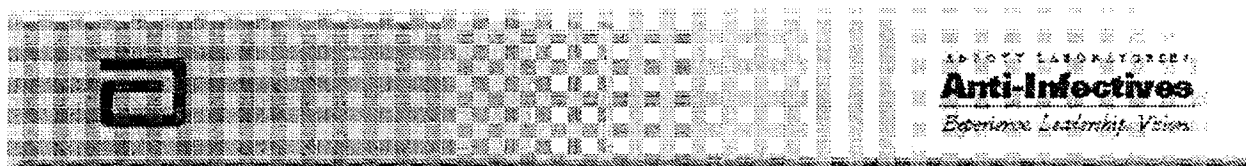
ABBT205187

## ***Bulk Drug Manufacturing Agenda***

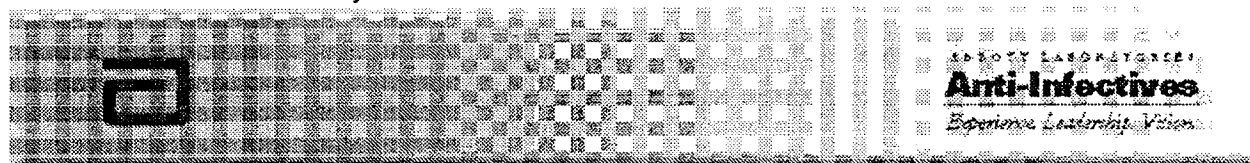
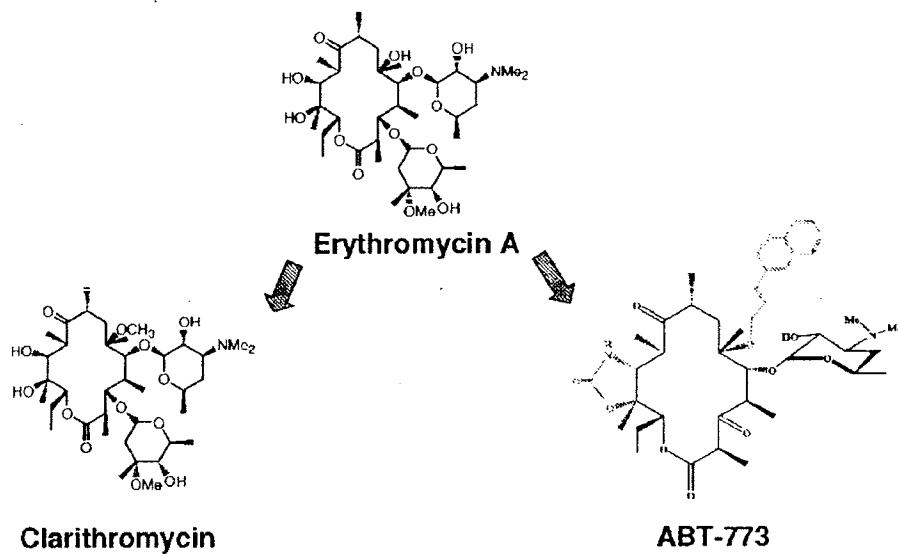
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### **Agenda**

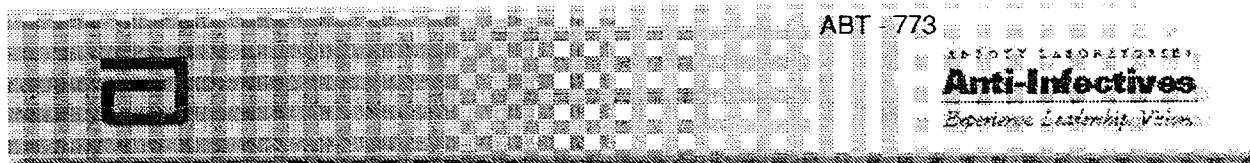
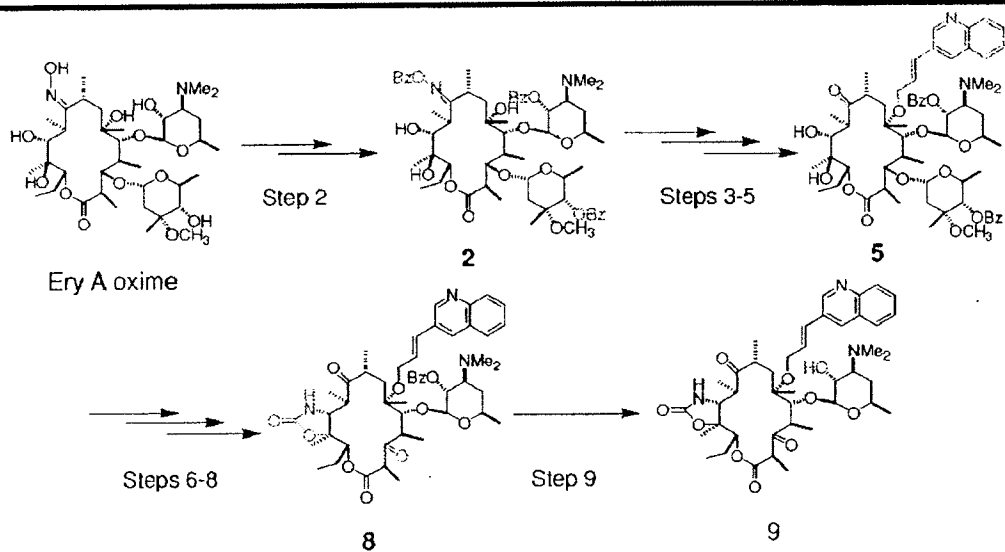
- Chemistry
- Process Strategy and Review
- Cost Review and Projection



**Bulk Drug Manufacturing**  
**Macrolide Structures**

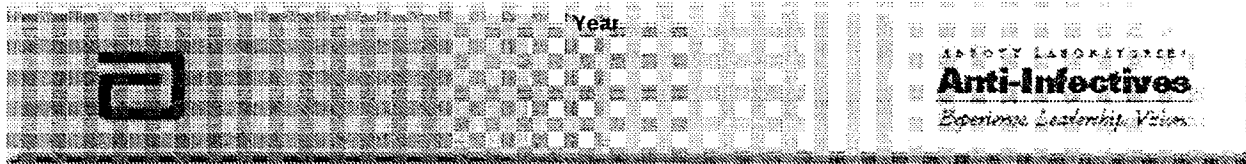
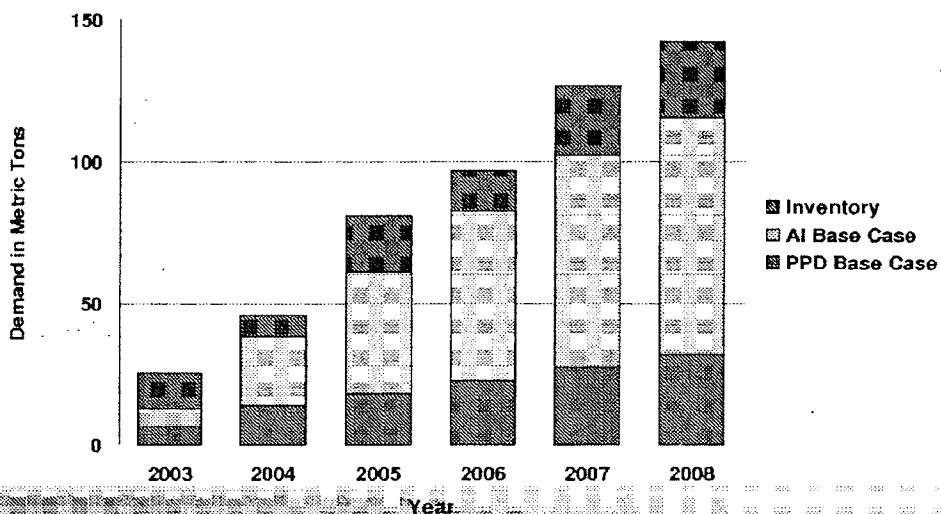


**Bulk Drug Manufacturing**  
**ABT-773 Synthesis**



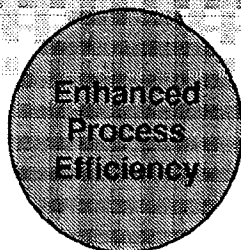
**Bulk Drug Manufacturing**  
Drug Substance Demand

**ABT-773 Bulk Demand - Consolidated LRP**

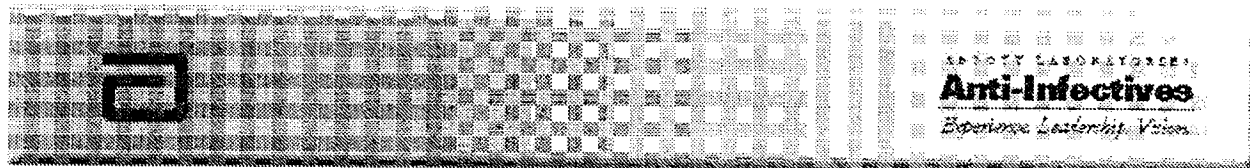


**Bulk Drug Manufacturing Process Improvements**

Cycle Time	Throughput	Side-chain Cost	Yield
------------	------------	-----------------	-------



	1998	1999	2000
CycleTime (Days)	53	35	30
Throughput Batch Size	100 kg	175 kg	350 kg
Manuf. Sites	1	5	5
Side-chain Cost	\$2500/kg	\$1100/kg	\$950/kg
Yield (%)	18	21	28



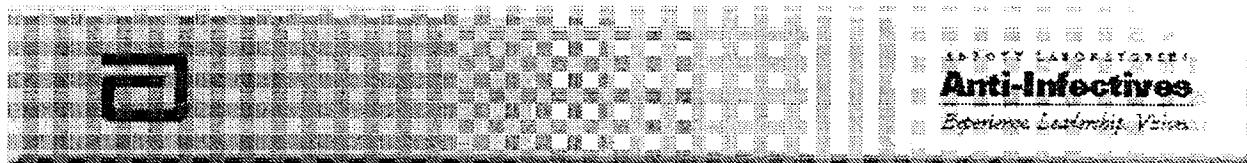
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ABBT205192

**Bulk Drug Manufacturing**  
*Comparison of Projected & Actual Demand/Cost*

---

		1999	2000	2001
Bulk Drug	Demand (kg)	1,400	2,520	1,675
	Actual (kg)	1,488	2,815	
Cost/kg	Projected (\$)	\$10,000	\$6,500	\$5,000
	Actual (\$)	\$7,800	\$5,400 (est.)	

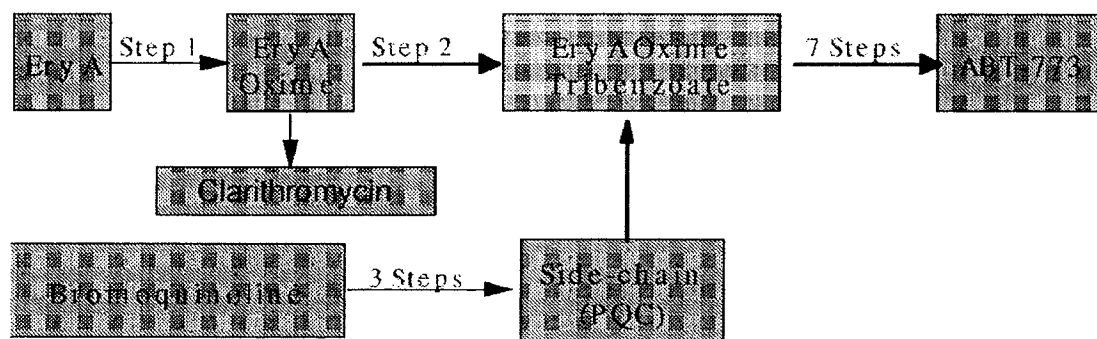


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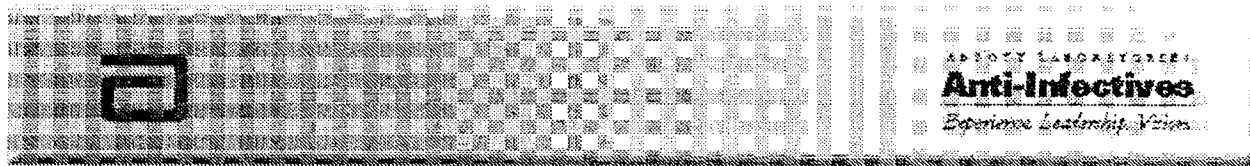
ABBT205193



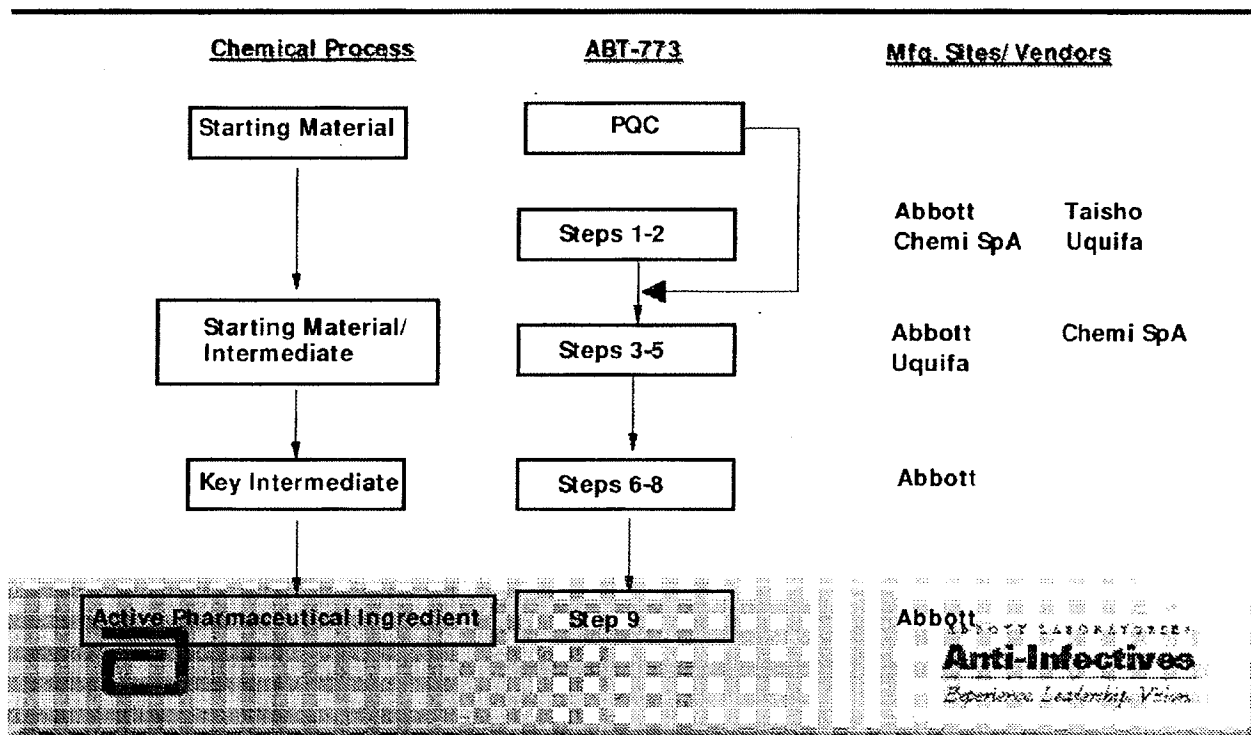
**Bulk Drug Manufacturing**  
*Synthesis*



- Bromoquinoline sources from India and China
- Side-chain outsourced from India and Europe
- Intermediates up to Step 5 outsourced/internal



**Bulk Drug Manufacturing**  
**Manufacturing Strategy: Starting Materials & Intermediates**



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ABB205195

**Bulk Drug Manufacturing**  
*Step 5 as Starting Material*

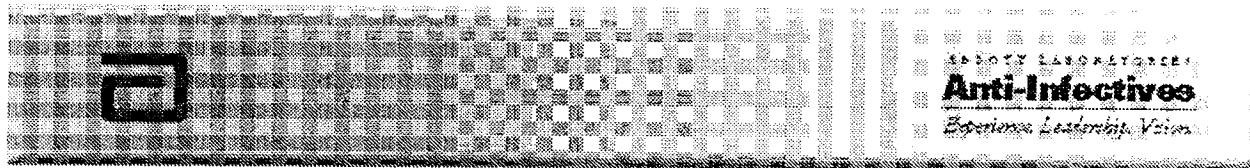
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**Criteria:**

Readily available at commercial scale  
Structure incorporated in Drug Substance molecule  
Well-characterized and known impurity profile  
Prepared by known methods

**Advantages:**

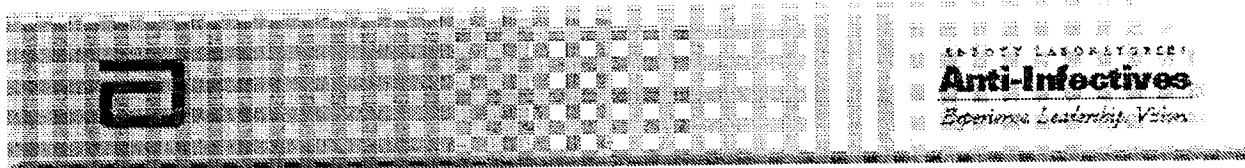
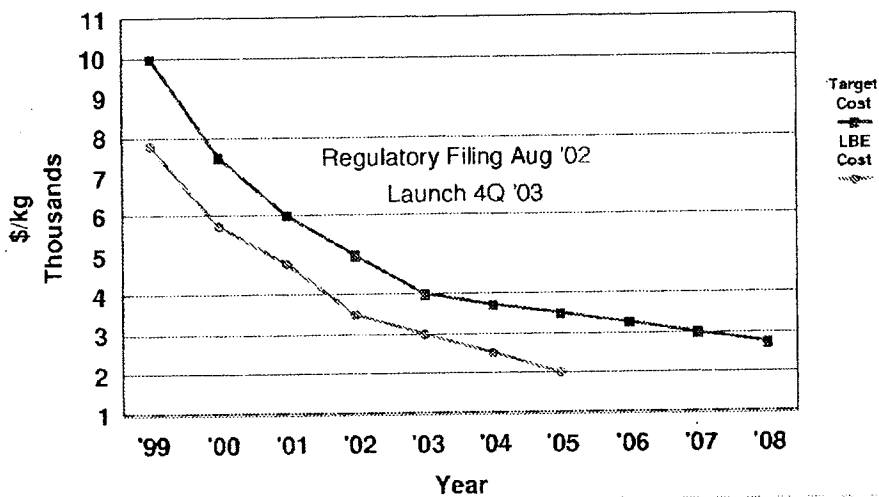
Commercial flexibility – additional manufacturers  
Process improvements (changes) without FDA prior approval  
Cost advantage



## Bulk Drug Manufacturing

Projected Bulk Drug Costs

Cost of Goods based on Current Process



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**Bulk Drug Manufacturing**  
*Projected Annual Capacity, Single Site*

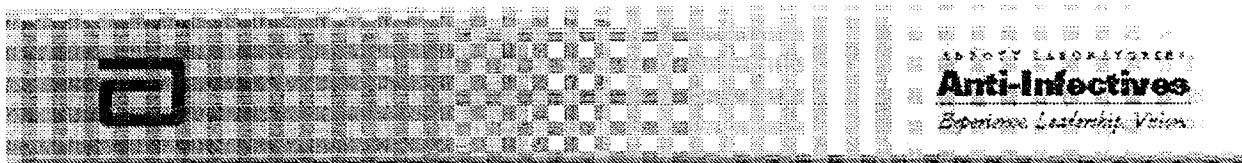
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Bldg C7A/ NC	15MT
Bldgs C17 and C7A/ NC	50MT

**Alternative strategies:**

Step 8 at vendor site(s)

Manufacturing in Abbott, Puerto Rico



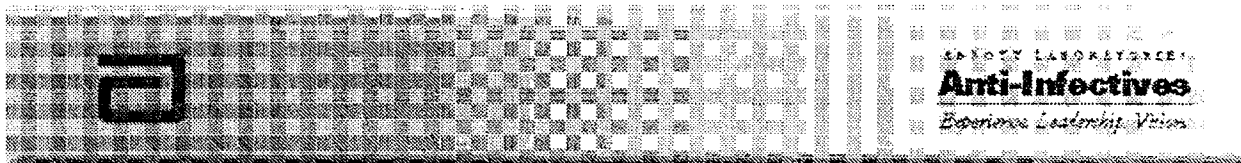
## **Bulk Drug Manufacturing**

### **Summary**

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#### **Summary**

- A viable process developed for commercial launch
- On track to achieve commercial target cost
- Identified strategies to meet long term bulk substance demand





PENGAD 800-631-6989

ABT-773 Ketolide Antibiotic - Tablet

[illegible]

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**March 2001****ABT-773****Monthly Highlights – Key Project Progress**

- With the ending of the winter season, Phase III enrollment for CAP (189 actual) and sinusitis (253 actual) are behind projections. Ethics committee approvals in Europe are continuing, 178 (U.S. and EU) CAP sites now have drug and 66 EU site approvals are in process. For sinusitis, 84 (US and EU) sites have drug and 50 EU site approvals are in process.
- Further Phase III start up activities are ongoing in Central America, So Africa and So America for CAP and ABS for their winter seasons starting in May. As we proceed with the enrollment in the Northern Hemisphere during April, we will make a final decision on initiating these sites for enrollment to be as cost effective as possible.
- A strategy to address European and US requirements regarding QT intervals is being formulated and will be finalized in April.
- The initial Phase I study for the IV formulation is on target to start in early May. This study will enable us to evaluate the appropriate IV dose and evaluate injection site pain with the formulation prior to a Multiple Dose study. Timing for Phase I Go/No Go is planned for September.
- The CMC and Biopharm End of Phase II meeting targeted for end of April was delayed by FDA to May 1<sup>st</sup> due to the FDA advisory for Ketek at the end of April.
- The Japanese development strategy is currently being re-addressed in light of organizational changes and the status of CAP and Sinusitis dose selection decision.

**Next Quarter's Key Progress Markers:**

Key Progress Marker	Target Date
Hold CMC/Biopharm End of Phase II meeting with FDA.	05/31
Determine if Southern Hemisphere sites for CAP and ABS should be initiated as a contingency if US/European enrollment fails to meet 500 patient target.	04/30
Complete enrollment in CAP and ABS Dose selection studies to meet Dose Decision milestone in July, assuming US/Europe can meet 500 patient target.	06/01
Complete enrollment in ASP and ABECB comparator studies in the U.S.	06/01
Complete intermediate scale-up activities in the U.K. site for initial bioequivalence study between Abbott Park and U.K. mfg sites.	05/31
Initiate first Phase I study of IV formulation.	05/01
Results available for Japan Phase I Dose Ranging study to determine Japan dose for Phase III/III studies and potential Bridging strategy.	04/15

**Key Project Issues and Risks**

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact	Strategy/Progress	Area / Responsibility	Resolution Date Planned / Actual
Clinical enrollment challenges due to a) delay in end of phase II meeting from September to November at request of FDA b) delay in start of study due to protocol changes requested by FDA c) light 2000-01 flu/respiratory season	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Critical path trials to development timeline are CAP & sinusitis, with dose decision for these indications needed by 7/2001 to maintain current timeline. Actual enrollment is lagging predictions.	A decision to initiate the Southern Hemisphere sites will be made in April as a contingency should the US and Europe fail to meet enrollment targets for CAP and sinusitis. ASP and ABECB studies are not on the critical path.	Venture	7/2001

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March 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
150 mg QD vs BID dose decision in CAP/sinusitis.	Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing, while relatively minor commercial impact ex-US, represents significant commercial hurdle in US.	Decision must be made in light of QD vs BID CAP and sinusitis data (7/2001); DSG analysis is planned to facilitate decision; internal efforts to defend 150 mg QD dosing with data on potent ribosome binding properties of ABT-773 are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study.	Venture/NPD/DSG	7/2001
Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product.	FDA requested an acute tox study in dog to further evaluate cardiac effects and also discussed whether a Phase I study should be conducted in subjects with underlying cardiac disease. A QT strategy is under development to be finalized in April.	Regulatory	6/2002/
Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch.	<input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Ability to define step 5 as the starting material will allow us to make further process improvements to reduce the cost of the bulk drug.	The end of Phase II package outlining our plans for starting materials was submitted to FDA on March 1. Meeting date has been postponed by FDA due to FDA advisory planned for Ketek at the end of April. New meeting date is May 1.	SPD	04/2001
The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially, particularly with respect to <i>H. influenzae</i> .	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Support by PK/PPD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model.	PK/PPD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PPD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. Dose decision for CAP & sinusitis expected 7/2001. To address this issue and potentially create a new model for evaluating PK/PPD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study.	Venture/NPD	07/2001

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March 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact — Cost — Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim.	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual 06/2002
Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .		FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required. CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim. The Phase I study to evaluate the IV formulation prototype will initiate in May 2001.	Venture	
Due to the dose change in the base development program, Phase I was repeated in Japan to further evaluate dose-ranging. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. Phase I results and Dose selection decision are needed prior to a Kiko meeting to discuss the Phase II/III strategy. <b>The Japanese development strategy will be re-evaluated in light of the organizational changes and dose selection decision timeframe.</b>	Japan	08/2001/
The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed.	<input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding.	The single-rising dose Phase I studies for the IV has been funded to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements. <b>It will start on May 21st. A Go/No go decision on the IV formulation is planned for Sept. 2001.</b>	HPD, Venture	09/2001

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**March 2001****ABT-773****Key Activities**

Activity	Commercial	LBE	Actual
Completion of study tracking intranet		2001	
Integration of intranet into communication plan		2001	
Integration of intranet into draft product label		2001	
Identification of communication vendor		2001	
Submission of brand/USAN names		2001	USAN submitted 3/01
Preliminary qualitative positioning research		4001	
Quantitative market research to support revised forecast		4001	
Preliminary qualitative positioning research		4001	

Activity	Formulation	Plan	Plan Date: 12/98	Actual
Phase I Formulation (Caps)*		12/1997		12/1997
Phase II Formulation (Tablet)		7/1999		8/1999
Clinical Supplies Phase IIB		7/1999		8/1999
Phase III Formulation (Tablet)		4/2000		7/2000
Phase III Clinical Supplies Manufactured		9/2000		9/2000
NDA Lots (3) Completed		7/2000		01/2001
Completion of 1 Year Stability for NDA		8/2001		
Formulation Peer Review		11/2001		

Drug Substance	KG	Plan	Actual	Plan Date:	Actual Projected Cost/kg
Activity					

Toxicology Activity	Plan Start 7/1997	Actual Start Date	Plan Date: 12/98	Report Completed
2-week oral Rat/Monkey	7/1997	6/1997		9/1998
Acute Studies	8/1997	8/1997		12/1997
Mouse Lymphoma/Micronucleus	11/1997	11/1997		4/1998
1 Month Rat/Monkey	12/1997	12/1997		12/1998
Pregnant Rat/Rabbit RF	1/1998	1/1998		11/1998
SEG II Rat/Rabbit	3/1998	3/1998		2/1999
Guinea pig sensitization	11/1998	11/1998		2/1999
3 Month oral Rat/Monkey	9/1999	10/8/1999		8/2000
Seg I/III Rat	9/1999	10/8/1999		12/2000
IV Irritation studies, set 1	7/1999	7/15/1999		8/1999
IV Irritation studies, set 2	2/2000	2/2000		3/2000
IV 2-week Rat/Monkey Studies	6/2000	6/2000		01/2001
Neonatal/Juvenile Rat	10/1999	11/1999		7/2000

See the Following page for a  
summary of Bulk Drug  
deliveries in SPD.

\* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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**March 2001****ABT-773****SPD ABT-773 Bulk Drug Deliveries Update**

	Target Date	Amount	Delivery Date	Amount	Lot #	Amount after milling
Campaign 1	2/28/99	200 Kg	2/23/99	209 Kg	50-007-CA-00	207.5 Kg (2/26)*
Campaign 2a	6/15/99	140 Kg	6/17/99	131 Kg	54-702-NI-00	129.4 Kg (6/19)*
Campaign 2b	7/15/99	140 Kg	7/21/99	121.5 Kg	55-208-CB-00	119.3 Kg (8/4)*
Tox lot	8/30/99	5 Kg	8/25/99	6.1 Kg	55-718-NI-00	
Campaign 3a	9/30/99	160 Kg	10/8/99	170.5 Kg	58493CB00	138.4 Kg (10/16)*
Campaign 3b	10/21/99	160 Kg	10/11/99	176.5 Kg	58494CB00	169.5 Kg (10/16)*
Pilot run 1	*****	15 Kg	10/30/99	18.9 Kg	59763N100	no milling
Pilot run 2	*****	15 Kg	2/5/00	15.5 Kg	61790NI00	no milling
Pilot run 3	*****	25 Kg	1/30/00	27.5 Kg	62764CB00	27.3 Kg (4/18)*
Campaign 4	12/10/99	320 Kg	11/23/99	355 Kg	61741CB00	309 Kg (3/2)*
Campaign 5	12/30/99	300 Kg	12/16/99	300.5 Kg	60665CB00	269.2 Kg (3/3)*
Campaign 6	2/28/00	280 Kg	2/23/00	321 Kg	62796CB00	315.5 Kg (3/6)*
Campaign 6 (IV)	2/28/00	15 Kg	2/22/00	20 Kg	62797CB00	18 Kg (3/15)*
Campaign 7	3/30/00	300 Kg	4/10/00	370 Kg	63890CB00	361.2 Kg (4/18)*
Campaign 7 (IV)	3/30/00	5 Kg	3/29/00	19 Kg	63889CB00	17.2 Kg (4/11)*
Campaign 8	4/25/00	200 Kg	5/11/00	263 Kg	64970CB00	256.5 Kg (5/15)
Campaign 8 (IV)	4/25/00	15 Kg	4/25/00	19.8 Kg	64971CB00	17.7 Kg (5/11)*
Campaign 9	6/15/00	300 Kg	6/14/00	375.7 Kg	65064CB00	355.7 Kg (6/20/00)
Campaign 9 (IV)	6/15/00	15 Kg	6/5/00	18.1 Kg	65065CB00	16.7 Kg (6/9/00)*
Campaign 10	7/15/00	300 Kg	7/26/00	361.2 Kg	67176CB00	359.0 Kg (8/10/00)
Campaign 11	8/15/00	300 Kg	8/4/00	333.7 Kg	68285CB00	271.9 Kg (9/7/00)
Campaign 12	10/6/00	300 Kg	9/27/00	356 Kg	69458CB00	292.3 Kg (12/8/00)
Campaign 13	11/23/00	300 Kg	11/15/00	351.2 Kg	71665CB00	349.1 Kg (12/20/00)
				<b>Total (year 2000)</b>		
				<b>2,815.5 Kg</b>		
Campaign 14	1/28/01	300 Kg	1/26/01	327.5 Kg	73886CB00	318.9 Kg(02/13/01)
Campaign 15	2/10/01	330 Kg	1/14/01	354.9 Kg	71699CB00	353.8 Kg(02/02/01)

\* Weight after rework

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**March 2001****ABT-773****All Clinical Studies:**

Protocol Number	Phase	Study Name	Protocol Number	Phase	Study Name	Start 1 <sup>st</sup> Pt. Dosed	End (Last CRF In)	Patients			Start 1 <sup>st</sup> Pt. Dosed	End (Last CRF In)	Patients		
								Target	Current				Target	Current	
M99-048	II	Dose Ranging, ABECB				9/1/99	3/31/00	300	384						
M99-053	II	Dose Ranging, Sinusitis				9/1/99	4/30/00	300	292						
M99-054	II	Dose Ranging CAP				9/1/99	4/30/00	300	187						
M00-219	III	CAP, Dose Ranging				11/7/00	4/30/01	800	189						
M00-216	III	ABECB vs Azithromycin				11/7/00	4/30/01	600	335						
M00-217	III	ABECB vs Levofloxacin				11/7/00	4/30/01	500	16						
M00-225	III	Sinusitis Dose Ranging				11/7/00	4/30/01	600	253						
M00-223	III	Pharyngitis vs Penicillin 500mg TID				11/7/00	4/30/01	520	411						
M00-222	III	Pharyngitis vs Penicillin 500mg TID				11/7/00	4/30/01	520	6						

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**March 2001****ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

**Protocol:** M00-219 – Dose-Ranging CAP

**Objective:** Dose selection.

**ABT-773 Doses:** 150mg QD vs 150mg BID, 10 days

**Comparator Doses:** None

**Target Enrollment:** 800

**Status:** Currently enrolling

**M00-216 – Phase III ABECB vs Azithromycin**

**Safety & Efficacy**

**150mg QD, 5 days**

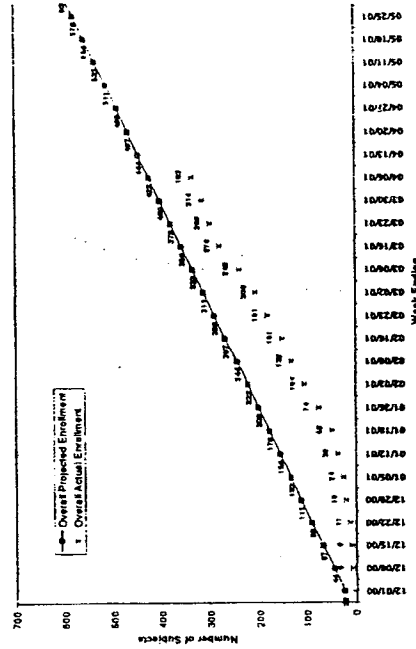
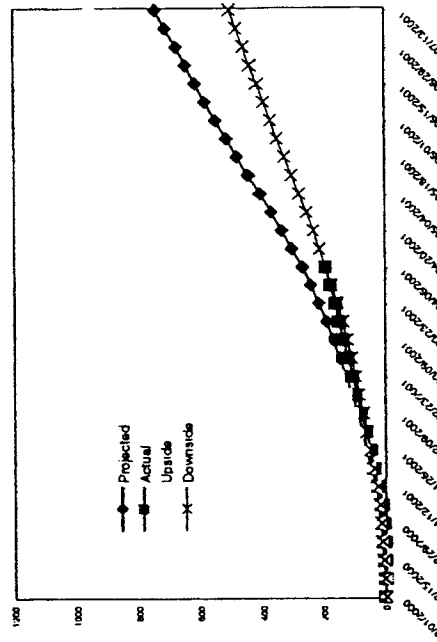
**Azithromycin 500mg day 1, 250mg QD for 4 days**

**600**

**Currently Enrolling**

**Major Findings:**

**Author:** (Download on clinicaltrials.gov)



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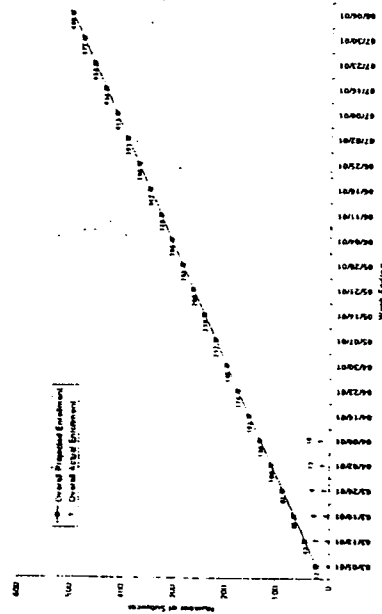
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March 2001

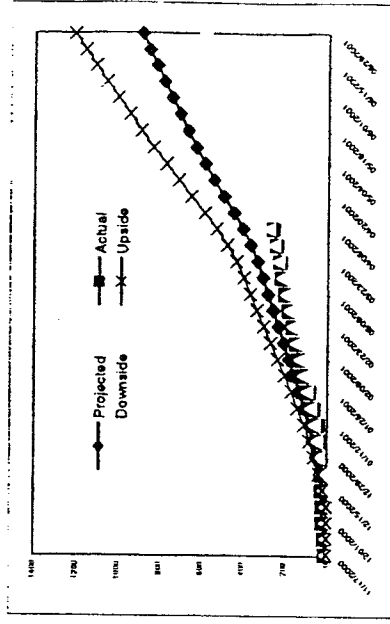
ABT-773

# Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

<b>Protocol:</b>	<b>M00-217 - Phase III ABECB vs Levofloxacin</b>	<b>M00-225 - Sinusitis Dose-Ranging</b>
<b>Objective:</b>	Safety & Efficacy	Dose Selection
<b>ABT-773 Doses:</b>	150 mg QD	150mg QD vs 150mg BID, 10 days
<b>Comparator Doses:</b>	Levofloxacin 500mg QD for 7 days	None
<b>Target Enrollment:</b>	500	600
<b>Status:</b>	Enrollment not yet started.	Currently enrolling
<b>Major Findings:</b>		



Author:  
(Double click on chart to edit)





**March 2001****ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)**Protocol:****M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID****Objective:**

Safety &amp; Efficacy

**ABT-773 Doses:**

150mg QD, 5days

**Comparator Doses:**

Penicillin 500 mg TID, 10 days

**Target Enrollment:**

520

**Status:**

Currently enrolling

**Major Findings:****M00-222 - Phase III Pharyngitis vs Penicillin 500mg TID**

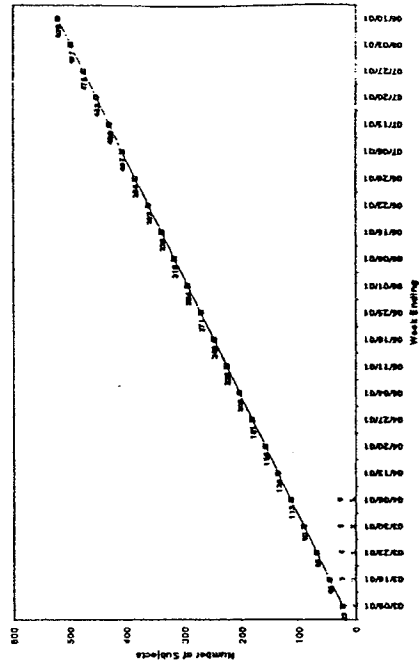
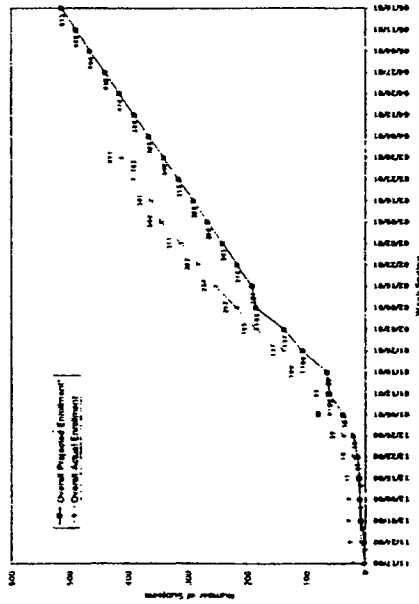
Safety &amp; Efficacy

150mg QD, 5 days

Penicillin 500mg TID, 10 days

520

Sites initiated, enrollment not yet started



D477Z:\MPSRs\ABT-773.doc

10 of 10

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# **ABT-773 Update**

## **March 19, 2001**

## **Agenda**

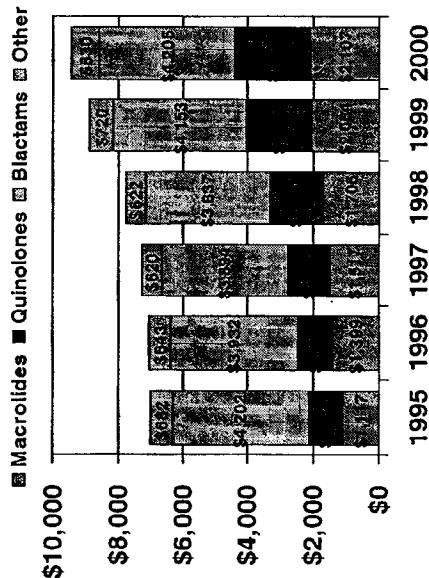
- **Market and trends**
- **Molecule**
- **Microbiology**
- **Pharm/tox**
  - **QT prolongation**
  - **Hepatotoxicity**
- **Clinical development**
  - **Phase I/II summary**
  - **Dose selection**
  - **Phase III program**
  - **Contingency plans**
- **Timeline and budget**
- **IV formulation**
- **Summary of key issues and action plans**

## Market and Drivers

- Infectious disease accounts for 13.3 million deaths yearly worldwide, 25% of all deaths
- Antibiotics are the 2<sup>nd</sup> most commonly prescribed category of drugs
- The global antibiotic market is a \$21B market, the 5<sup>th</sup> largest global market in sales
- The global antibiotic market has shown modest sales growth
  - 3.9% CAGR<sub>96-00</sub> in sales for overall combined market
  - 4.7% CAGR<sub>96-00</sub> in sales for branded combined market
- Sales growth in the U.S. has been driven by replacement of older generic agents with newer branded agents (most other markets show increasing generic use)
  - Antibiotic resistance results in OBSOLESCENCE of existing agents over time (a CHRONIC problem)
  - Sales per TRX rose from \$18.42 in 1995 to \$28.05 in 2000 (8.8% CAGR)
  - Generics still represent 61% of TRX, representing an opportunity for conversion
- Generics have been more stable ex-U.S

# U.S. Market Trends

## By Class

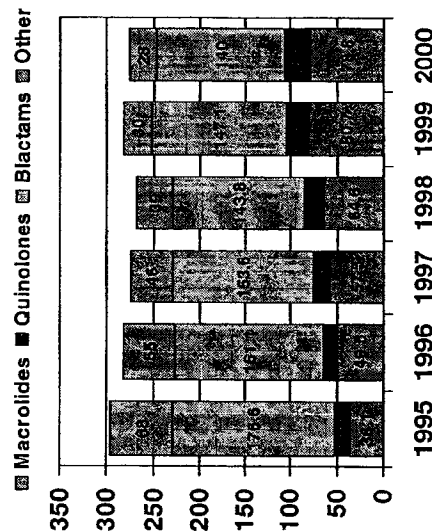


**SALES**

CAGR<sub>95-99</sub>: 6.1%

10.0% Branded

-5.5% Generic



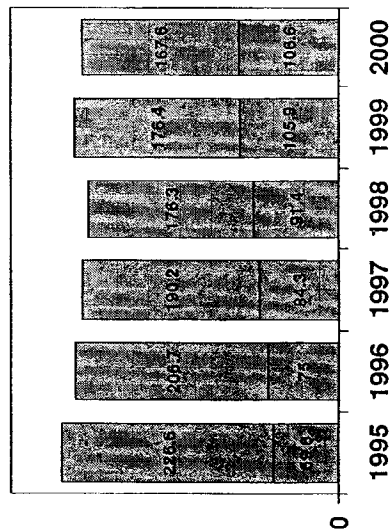
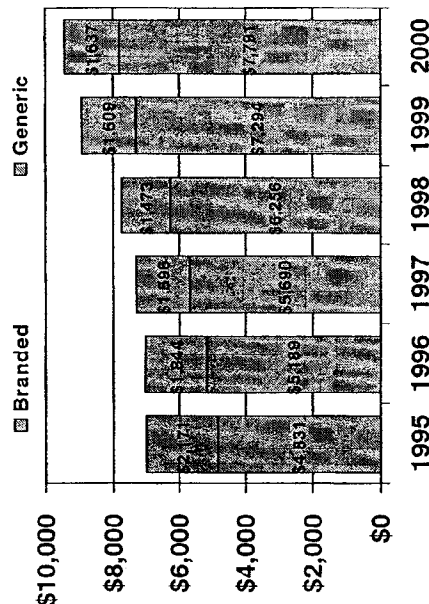
**TRX**  
(excludes IV)

CAGR<sub>95-99</sub>: -1.5%

8.9% Branded

-5.9% Generic

## Generic vs Brand



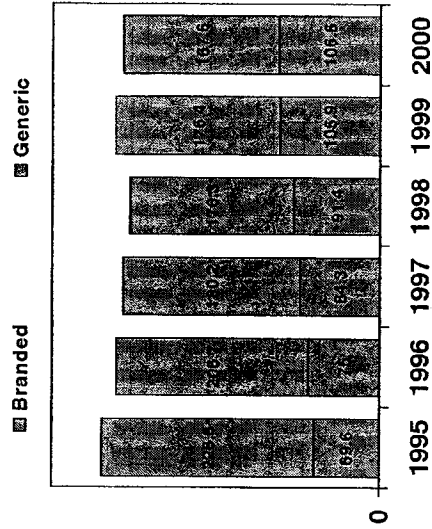
Macrolides and quinolones have driven the growth of the market

Generic use decreasing with increasing antibiotic resistance

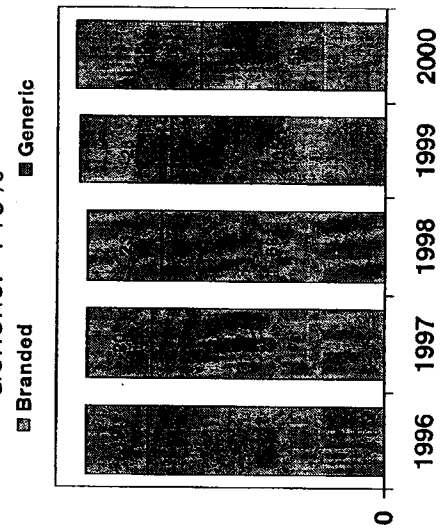
While most markets tend toward increasing utilization of generics, the antibiotic market is tending toward decreasing utilization of generics-OBSOLESCENCE

## Backup

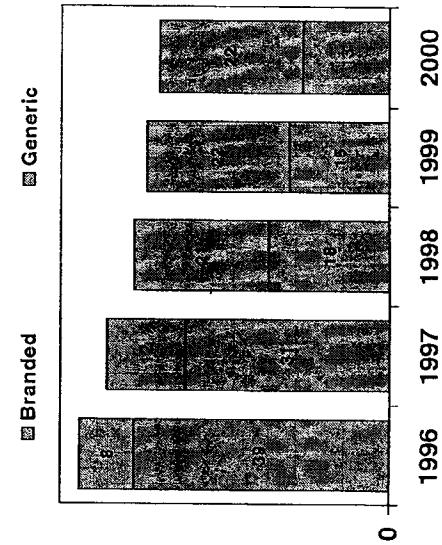
**Antibiotics**  
Brand: +9%  
Generic: -6%



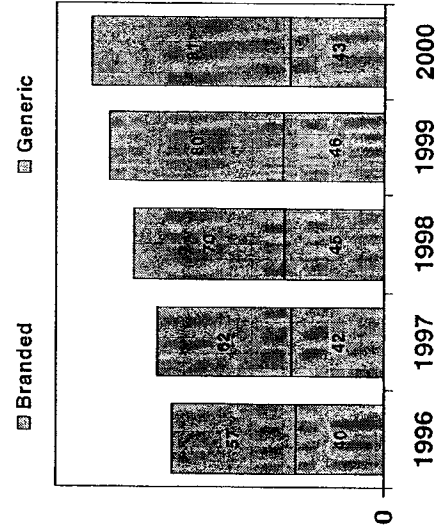
**Calcium Blockers**  
Brand: -6%  
Generic: +19%



**H2 Antagonists**  
Brand: -25%  
Generic: +29%



**Beta Blockers**  
Brand: +2%  
Generic: +13%

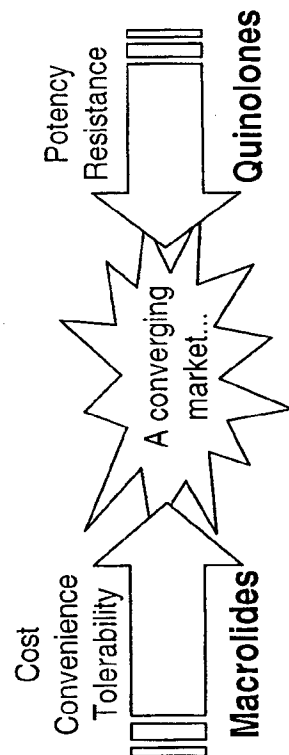


# Antibiotic Classes

3 antibiotic classes dominate the market, representing 89% of global sales

Class Dominant Brand	Other Brands	Global Class Sales (\$MM)	Ped	IV	Comment
B-lactam Augmentin	Ceftin, Cefzil, pens, amox	\$10,561	X	X	<ul style="list-style-type: none"> <li>•B-lactams 1.1% CAGR; -1.4% Y-Y</li> <li>•High generic penetration</li> <li>•Augmentin unique, due to resistance</li> </ul>
Macrolide Zithromax	Biaxin erys	\$4,066	X	X	<ul style="list-style-type: none"> <li>•Macrolides 8.1% CAGR; 2% Y-Y</li> <li>•Zithromax set new standards in cost, convenience, tolerability</li> <li>•Z growth has slowed (5% Y-Y) due to maturing brand and resistance</li> </ul>
Quinolone Levaquin	Cipro Tequin Avelox	\$3,750	Under Dev	X	<ul style="list-style-type: none"> <li>•Quinolones 11% CAGR, 10% Y-Y</li> <li>•Leveraging macrolide resistance to become fastest growing class</li> <li>•New quinolones have overcome narrow spectrum and poor tolerability</li> </ul>

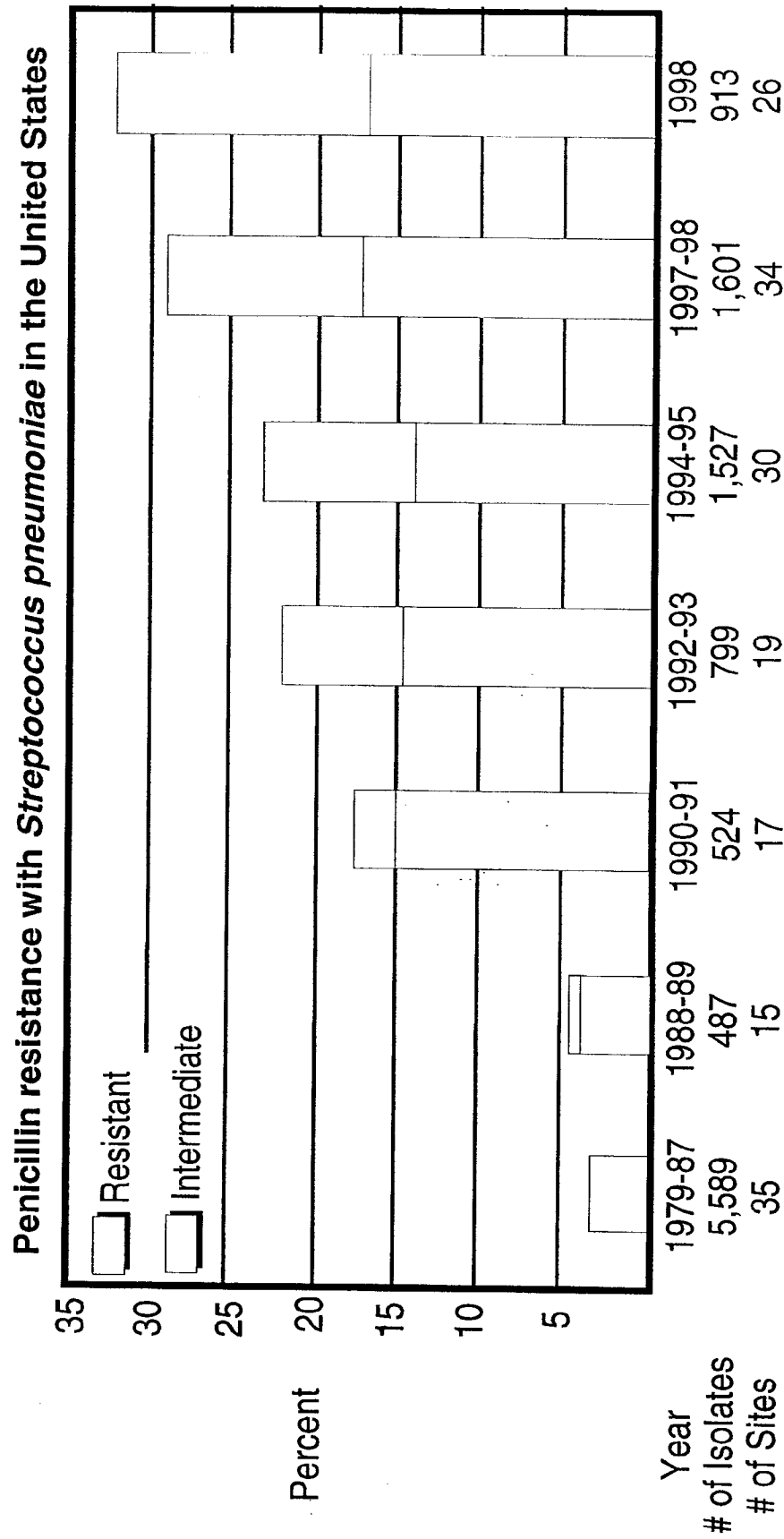
CAGR = Global 1995-2000 compound annual growth rate



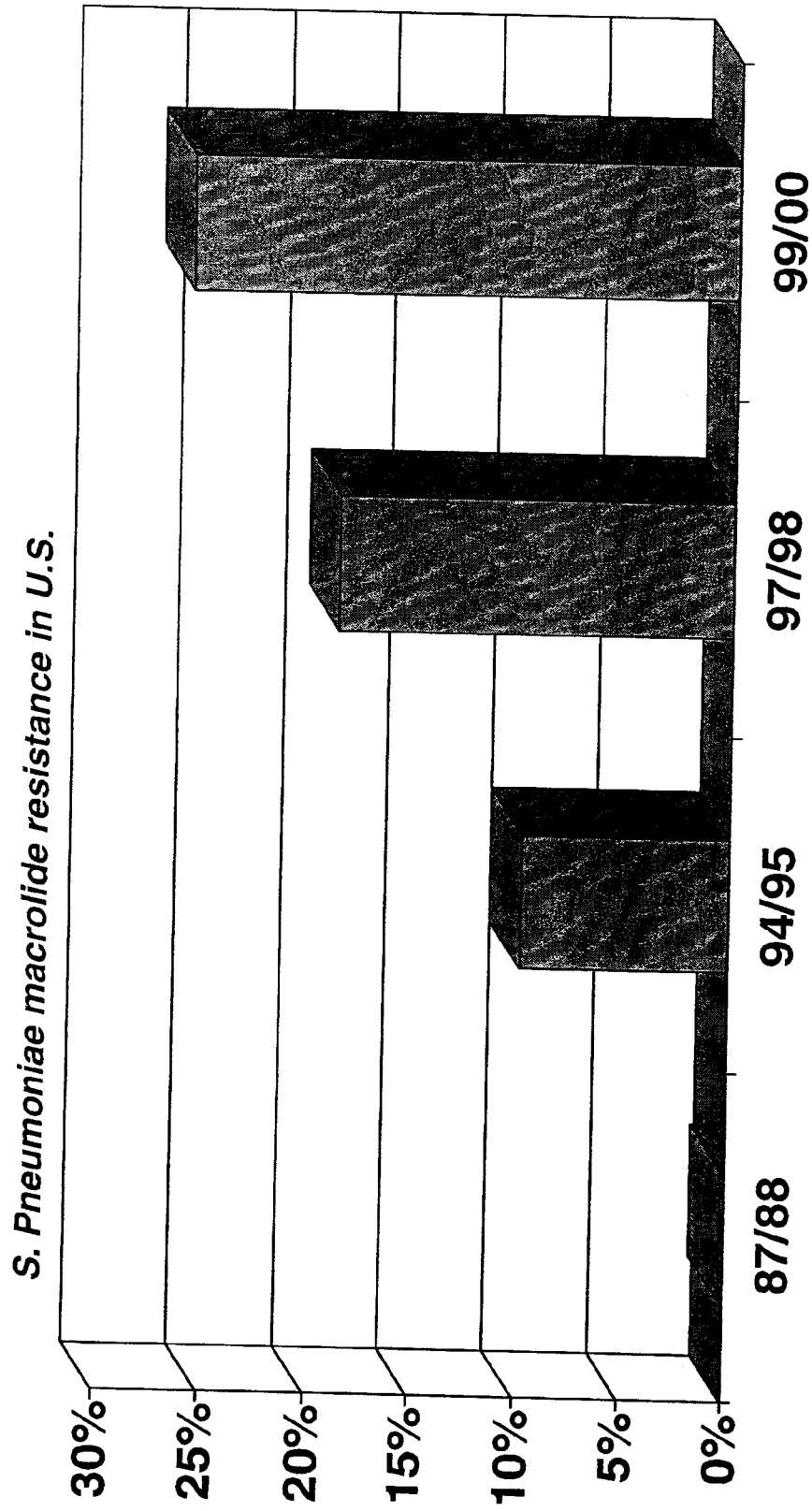
- Macrolides expanded the market on the basis of Pen/B-lactamase resistance, cost, convenience, and tolerability
- Quinolones (+11% CAGR) are now driving the market from a macrolide resistance standpoint (while near parity on cost, convenience, tolerability)



**Biaxin and Zithromax were able to leverage increasing Pen resistance to create a compelling selling proposition**



Quinolones are now leveraging macrolide resistance in the same fashion to become the fastest growing class

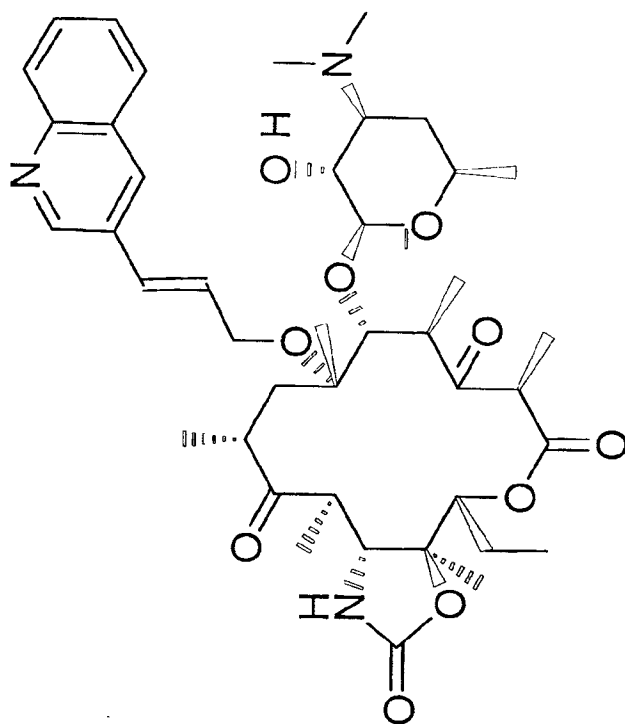


# ABT-773 Target Profile

	ABT-773	Levaquin	Zithromax
Convenience	Target is QD dosing all indications Potential for BID in CAP & sinusitis  Duration: 5d, 10 d (parity to Zithromax) <b>PARITY IF QD</b>	All RTI regimens 500 mg QD, 7-14 d	250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP
Efficacy	Statistically equivalent cure/eradication to comparators; can take advantage of macrolide/penicillin resistance <b>PARITY</b>	Statistically equivalent cure/eradication to comparators; gold standard for CAP with IV; can take advantage of macrolide/penicillin resistance	Statistically equivalent cure/eradication to comparators; availability of IV adds to efficacy image; subject to increasing levels of macrolide resistance
Activity	Most active agent for Gram + pathogens, including telithromycin; parity for atypicals; parity to Zithromax for Gram -, through inferior to quinolones (weakness)	Highly active against most clinically relevant respiratory pathogens; potential issue with increase in Gram - resistance; theories that Gram + quinolone resistance may increase dramatically/rapidly with increased use	Not as active as clari in Gram + pathogens, increasing macrolide resistance, moderate Gram - activity
Adverse Events	Taste perversion: 4% Diarrhea: 10% <b>COMPARABLE TO BIAxin XL</b>	Very well tolerated and safe	Very well tolerated; GI disturbance ~ 2-5%; no taste perversion
Resistance Claim	Being pursued; important to development of resistance story; availability of IV will increase likelihood of claim	Claim for pen-R Strep. pneumo	None
Price	Parity to Zithromax	\$60 for 7 days	\$43 for 5 days
Other	Attempt to leverage "best of both worlds" message i.e. potency & resistance coverage of a quinolone with safety & appropriateness of macrolide	Some class-related negative perceptions among some physicians with respect to AEs and appropriate use, but with increased use these barriers are eroding	

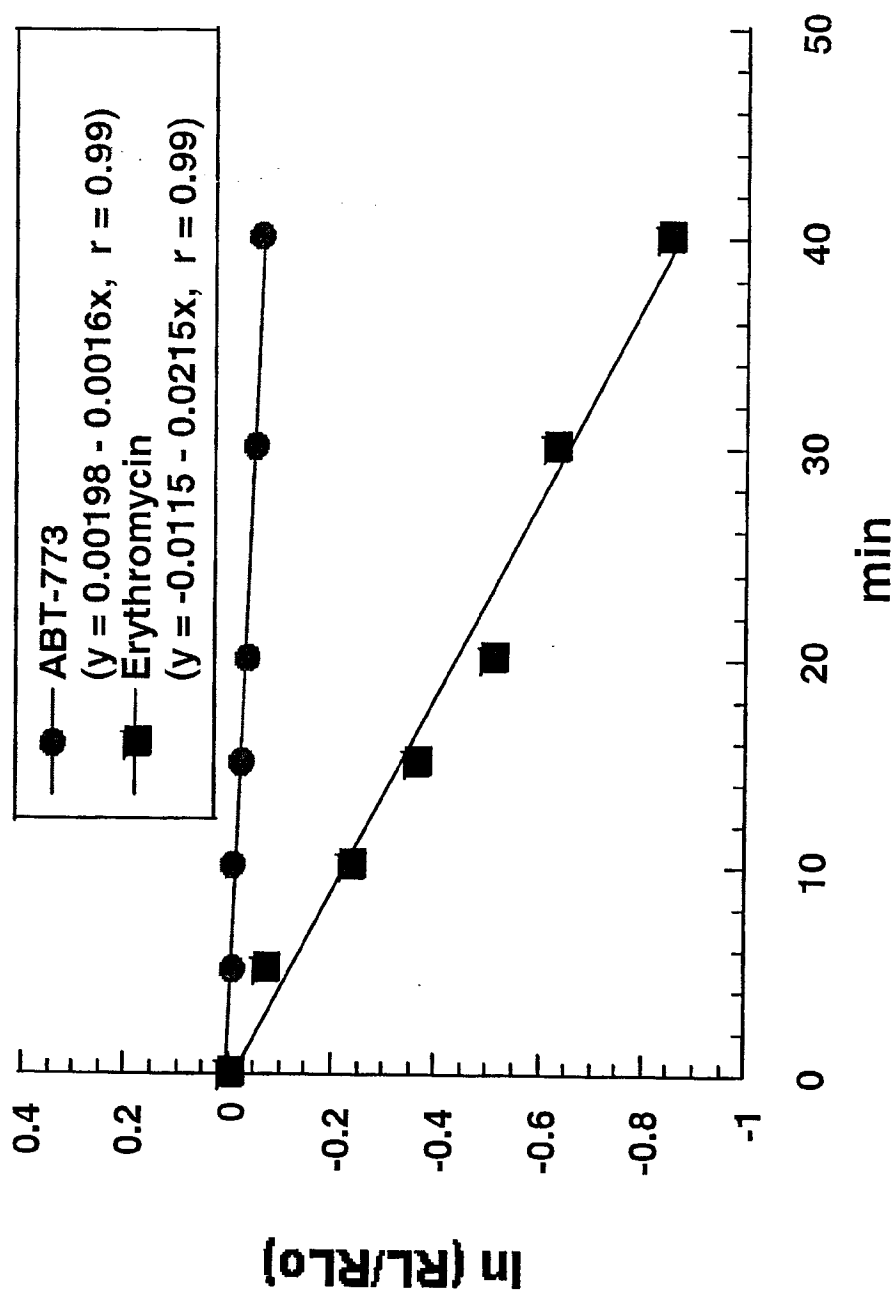
# ABT-773 SAR

- Quinolylallyl propenyl moiety at the 6-0 -position (↑ PK, activity)
- Carbamate group at the 11, 12-position (↑ activity vs macrolide-resistant Strep)
- Keto group at the 3-position (confers *erm* non-induction)



- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.

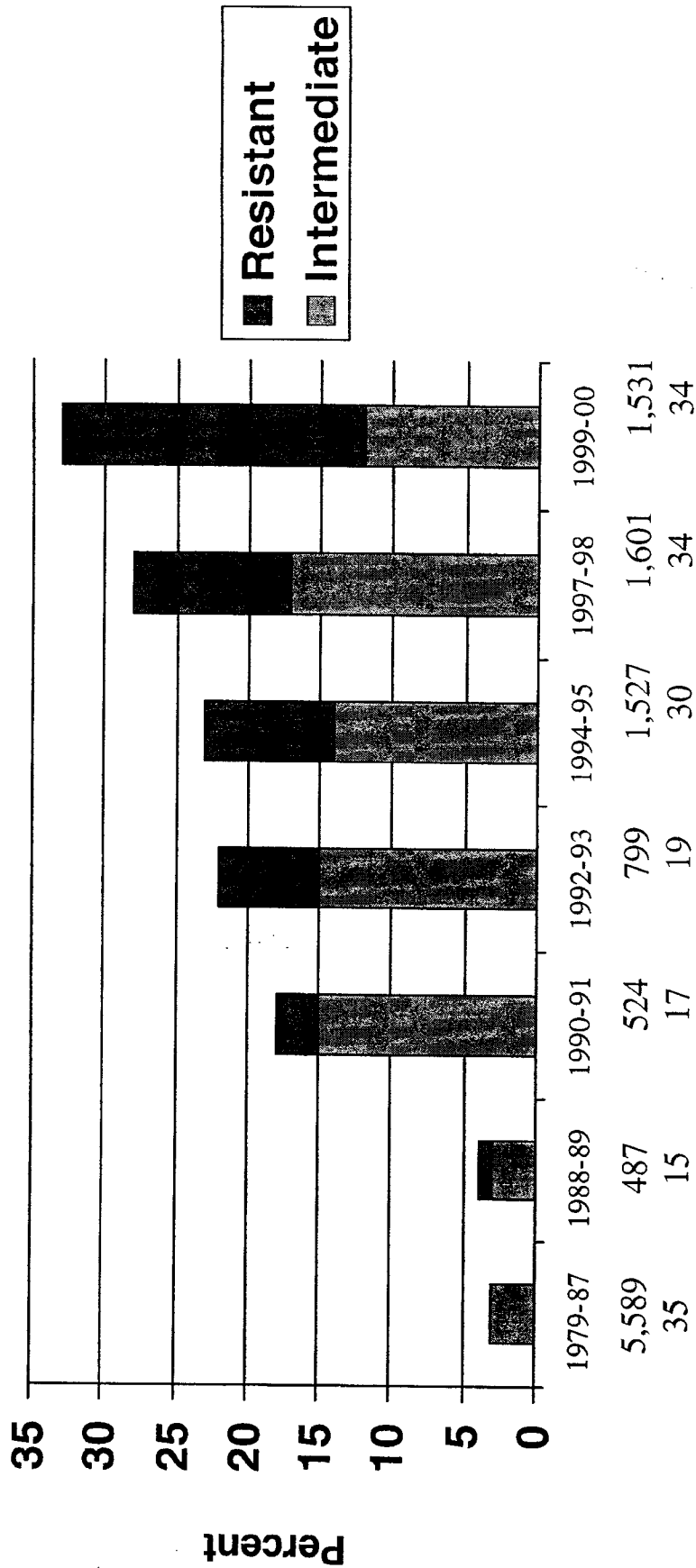
# ABT 773 Microbiology

MIC90	Clari	Trovan*	Ketek	ABT-773
S. Pneumoniae (susc)	< 0.03	0.125	0.008	< 0.002
S. Pneumoniae (mef)	8.0	0.125	1	0.12
S. Pneumoniae (erm)	> 32	0.125	0.12	0.01
S. Pyogenes (mef)	16	0.125	1	0.12
S. Pyogenes (erm)	> 32	0.25	> 8	0.5
M. catarrhalis	0.03	0.015	0.25	0.25
H. influenzae	8	0.015	2	2

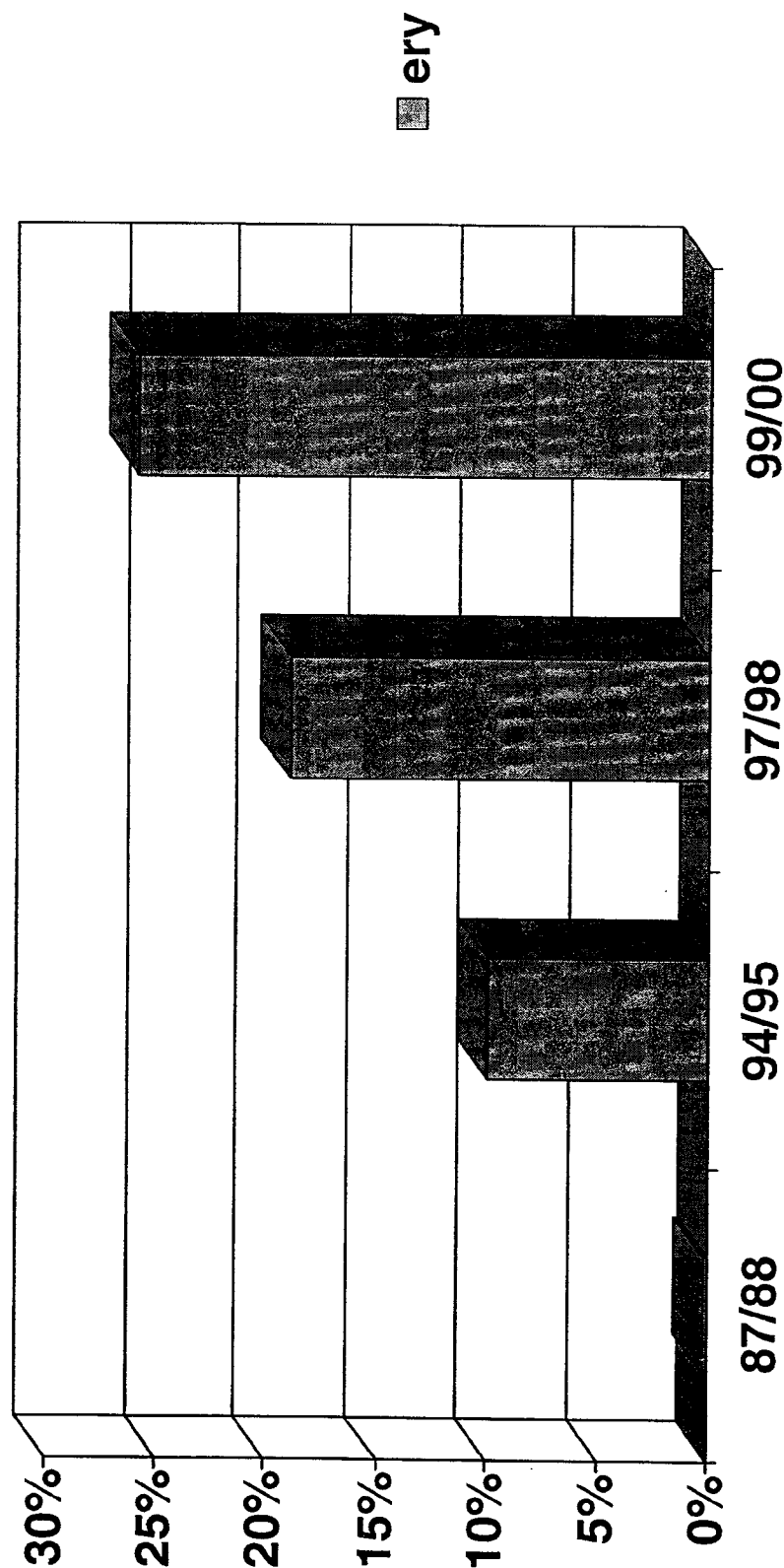
\* Withdrawn from market, but among the more potent quinolones

# Microbiology

## Penicillin resistance with *Streptococcus pneumoniae* in the United States



# *S. pneumoniae* Macrolide Resistance from U.S. Surveillance



US surveillance studies: Doern et al.



# Preclinical/Clinical Issues

- QT prolongation
- Hepatotoxicity

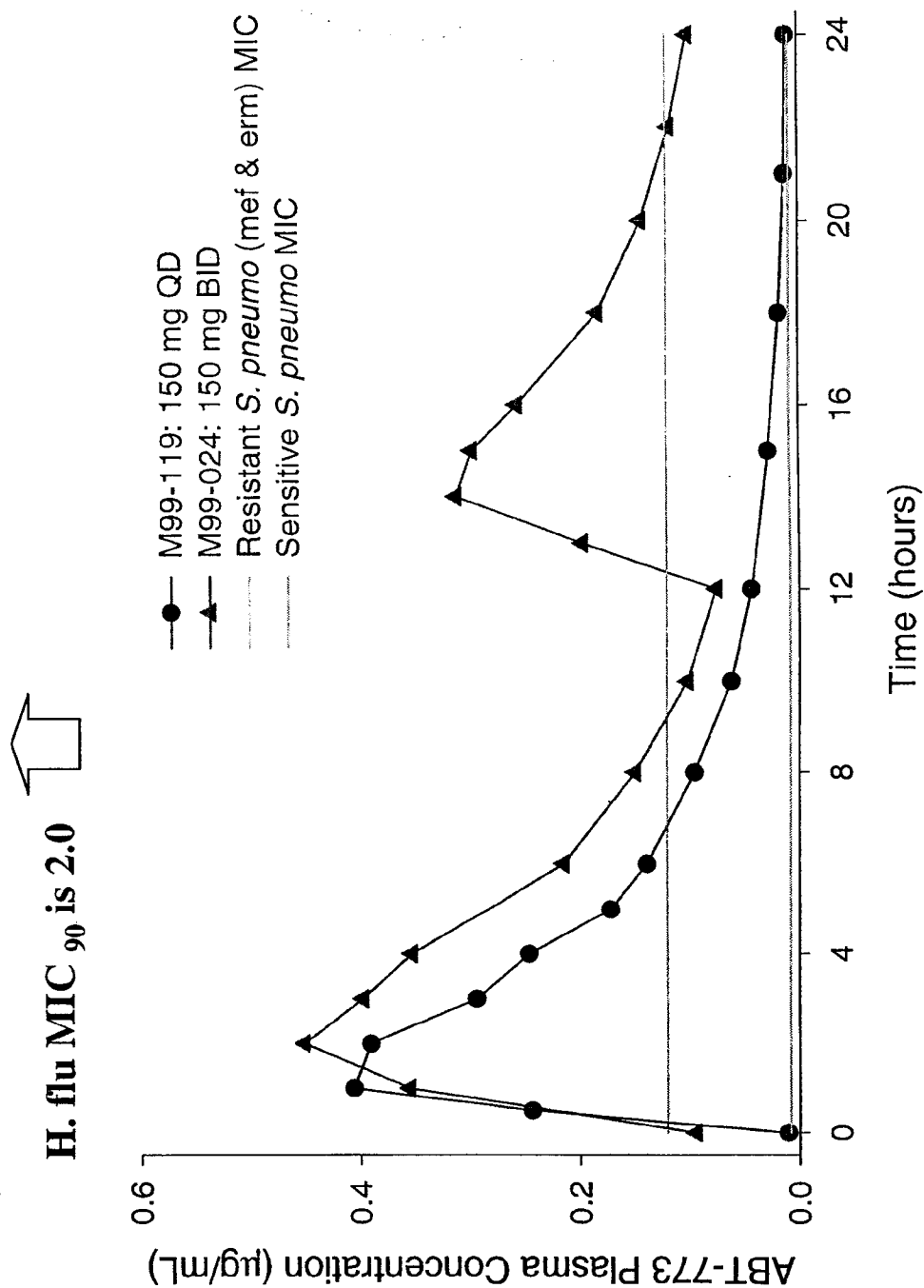
# QT Prolongation

- **Purkinje fiber repolarization**
  - APD increase at 5 mcg/mL (10x clinical Cmax) in the absence of plasma proteins, but not in their presence
  - Moxi > Clari > Ery ~ ABT-773 > Levo (without plasma)
- **Dogs**
  - no significant effect on QTc up to 9 mcg/mL
  - 11% increase (40 msec) at 22 mcg/mL
  - Telemetry-instrumented dog study requested by FDA will be completed by May 1, 2001
- **Humans**
  - Possible dose effect in Phase I at daily dose > 800 mg
  - No significant QT effect in ketoconazole interaction study
  - No clinically relevant QT effect in Phase II studies 150 – 600 mg daily (n=412)

# Hepatotoxicity

- Toxicology studies
  - NTEL for LFT abnormalities in rat = 3-8 x clinical AUC
  - NTEL for LFT abnormalities in monkey = 2-4 x clinical AUC
- Clinical experience
  - No evidence of LFT issue in Western subjects (<1% asx LFT elevation in >1000 pts in phase II-III studies)
  - Japanese in bridging study showed increased LFTs.
    - 7 of 42 (17%) Japanese subjects had >3x ULN
    - No evidence of dose response
    - Repeat study in Japan showed no evidence of LFT increases in Japanese (n=60) or Caucasians (n=8).

# ABT 773 Pharmacokinetics



# Phase II Clinical Studies

Study	Dose/Duration	Number of subjects
ABECB	150, 300 or 600 mg OD Duration: 5 days	N = 384
Acute Sinusitis	150, 300, or 600 mg OD Duration: 10 days	N = 292
CAP	300 or 600 mg OD Duration: 7 days	N = 187

# Phase II Results

## Combined ABECB, CAP, ABS Clinical Response

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

# ABT 773 Phase II Findings

## Combined ABECB, CAP, ABS Adverse Events

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
<b>GI and Taste</b>			
<b>Taste Perversion</b>	4% (8/223)	17% (55/322)	27% (87/318)
<b>Diarrhea</b>	10% (22/223)	11% (34/322)	19% (60/318)
<b>Nausea</b>	5% (12/223)	12% (40/322)	26% (83/318)
<b>Vomiting</b>	2% (4/223)	6% (19/322)	14% (44/318)

# Phase II: 150 mg QD vs 300 mg QD

Phase IIb Data: Intent-to-treat									
		Bronchitis		CAP		Sinusitis		Total	
Clinical Cure	150 mg QD	85%	104/123			82%	72/88	83%	176/211
		83%	107/129	84%	80/95	80%	72/90	82%	159/314
	Bacteriological Cure	H. flu	89%	17/19			60%	3/5	83%
81%			17/21	100%	9/9	100%	7/7	89%	33/37
S. pneumo		77%	10/13			100%	3/3	81%	13/16
		90%	9/10	82%	14/17	100%	8/8	89%	31/35



# Community-Acquired Pneumonia

## Clinical Response

	300 mg	600 mg
--	--------	--------

Clin and Bact. Eval	92% (54/59)	82% (47/57)
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Clin Eval	92% (72/78)	80% (56/70)
-----------	-------------	-------------

ITT	84% (80/95)	73% (65/89)
-----	-------------	-------------

# Phase II summary

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD selected for ABECB and pharyngitis in pivotal phase III comparative studies
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

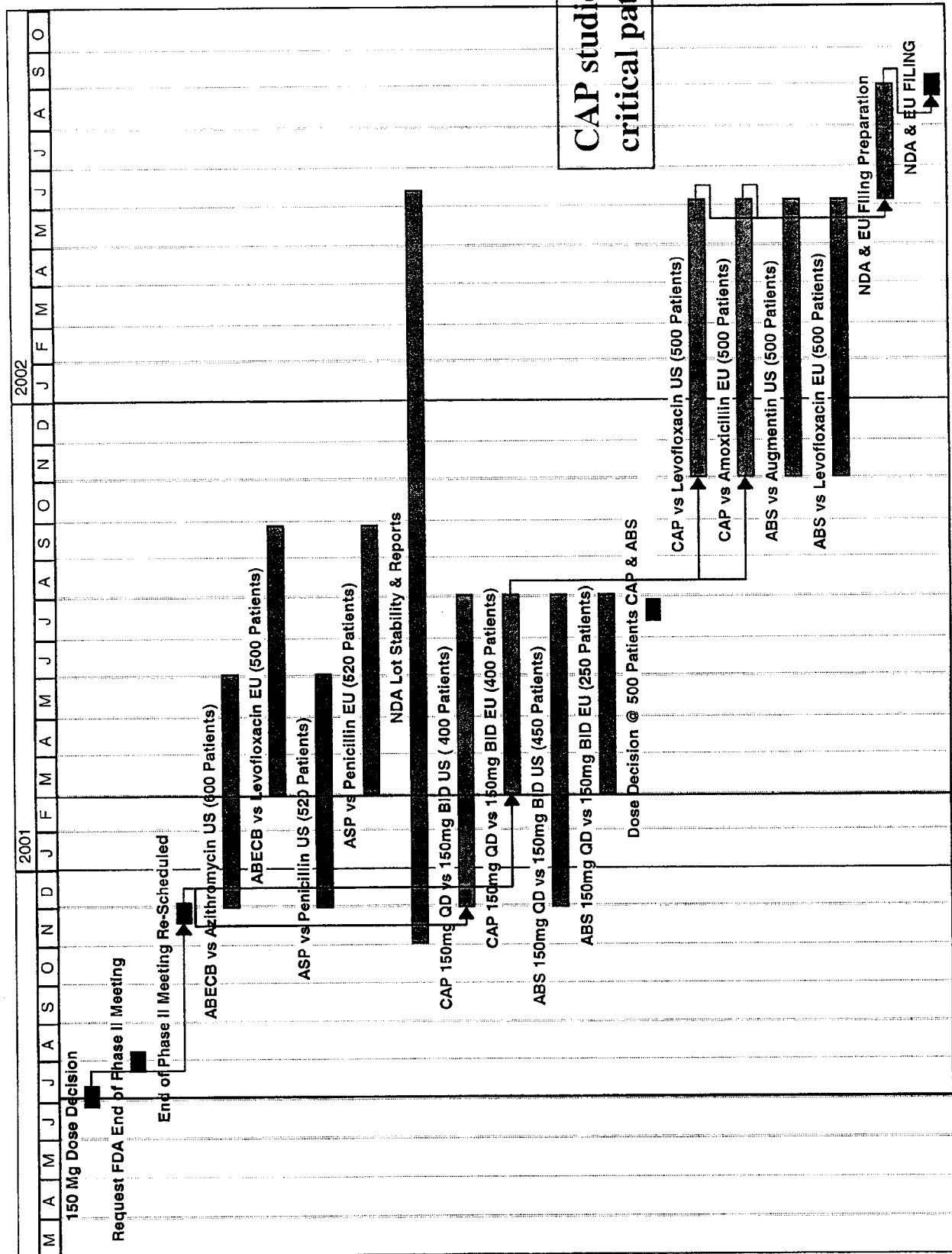
## Dose selection: Divergent U.S. and European regulatory and commercial considerations

- **US**
  - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
  - Approval on indication-by-indication basis
- **Europe**
  - Relatively minor commercial impact of BID dosing
  - CAP indication is critical for overall approval

# ABT 773 Indications

<b>Infection</b>	<b>Dosage</b>	<b>Duration</b>
Pharyngitis/Tonsillitis (ASP)	150 mg QD	5 d
Acute bacterial exacerbation of chronic bronchitis (ABECB)	150 mg QD	5 d
Acute bacterial sinusitis (ABS)	150 mg QD or BID	10 d
Community-acquired pneumonia (CAP)	150 mg QD or BID	10 d

# ABT 773 Development Timeline



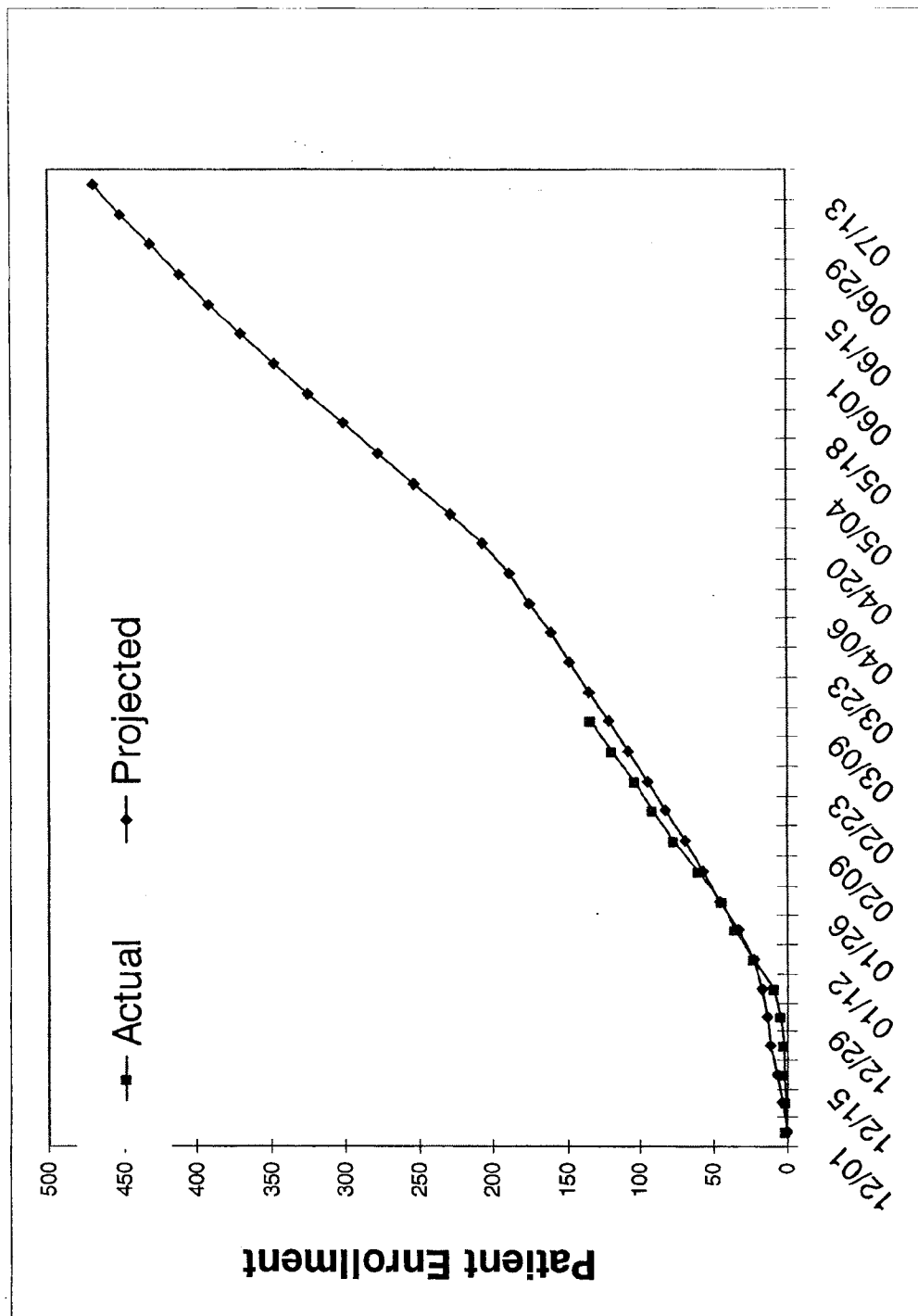
## Phase III: ABECB and ASP

Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-216 ABECB vs Azithromycin	600	Nov. 2000	US	277	110
M00-217 ABECB vs Levofloxacin	500	Jan. 2001	EU	2	100
M00-222 ASP vs Penicillin	520	Jan. 2001	EU	1	45
M00-223 ASP vs Penicillin	520	Nov. 2000	US	337	45

# Phase III: CAP and ABS

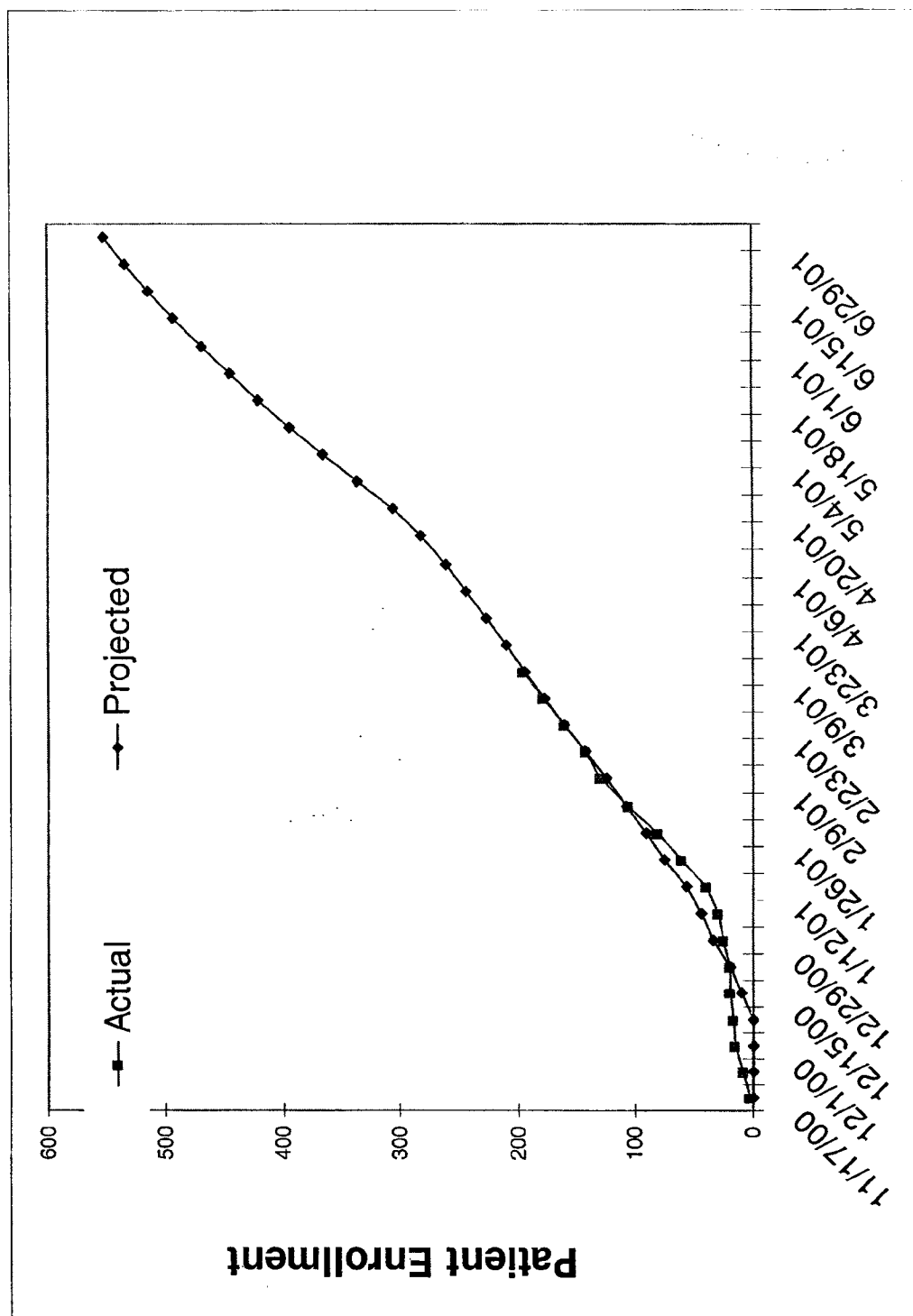
Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-219 CAP 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	143	294
M00-221 CAP vs Levofloxacin	500	Nov. 2001	US		200
M00-220 CAP vs Amoxicillin	500	Nov. 2001	EU		200
M00-225 ABS 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	205	114
M00-218 ABS vs Augmentin	500	Nov. 2001	US		90
M00-226 ABS vs Levofloxacin	500	Nov. 2001	EU		90

# CAP dose-ranging study: enrollment status





# Sinusitis dose-ranging study: enrollment status



# Progress towards resistance claim

Pathogen	M00-216 ABECB	M00-219 CAP	M00-225 ABS
Subjects with Positive culture	266	60	77
<i>S. Pneumoniae</i> isolates	16	16	19
Resistant <i>S.pneumo</i>	7	9	7
<i>Penicillin resist</i>	0	1	1
<i>Macrolide resist</i>	2	0	3
<i>PRSP &amp; MRSP</i>	5	8	3
# of isolates proposed for resistance claim			
PRSP	15	15	15
MRSP	15	15	15

# ABT 773 Contingency Plan

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
- Dose decision delayed to Sept 2001, filing delayed
- Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere

# 2001 Clinical Budget (\$MM)

• 2001 Clinical Program	61.7
• Assumptions to achieve budget	
• Complete 2000/01 Phase III Studies by June 2001 in U.S. and Europe	
• Initiate 2001/02 Phase III Studies by Nov. 2001	
• Conduct start up activities <b>only</b> in Southern Hemisphere, <b>do not</b> initiate enrollment	
• Contingency costs	2.0
• Assumptions	
• Continue European ABECB and ASP studies to Dec 2001	
• Enroll CAP and ABS studies in the Southern Hemisphere through Sept. 2001	
• Partial cost offset due to lower enrollment in U.S. and Europe	

# Other Filing Options

*Other filing options have been evaluated and are less desirable (regulatory, commercial, logistic)*

Option	Indications	Dose	Filing Date US	Filing Date Europe
Option 1 File without CAP indication in the U.S., delay Europe filing	ABECB/ASP/ABS	150mg QD	Aug 2002	June 2003
	CAP	150mg QD or BID	Aug 2003	June 2003
Option 2 Make BID dose decision for CAP and ABS now.	ABECB/ASP	150mg QD	Aug 2002	Aug 2002
	CAP/ABS	150mg BID	Aug 2002	Aug 2002
Option 3 Delay Dose Decision to Phase III	ABECB/ASP/ABS 3 arm CAP Study	150mg QD or BID	Dec 2002	Dec 2002
Option 4 Run separate US and European clinical programs	ABECB/ASP	150mg QD	Dec 2002	Aug 2003
	CAP/ABS	150mg QD US 150mg BID Europe	Dec 2002	Aug 2003

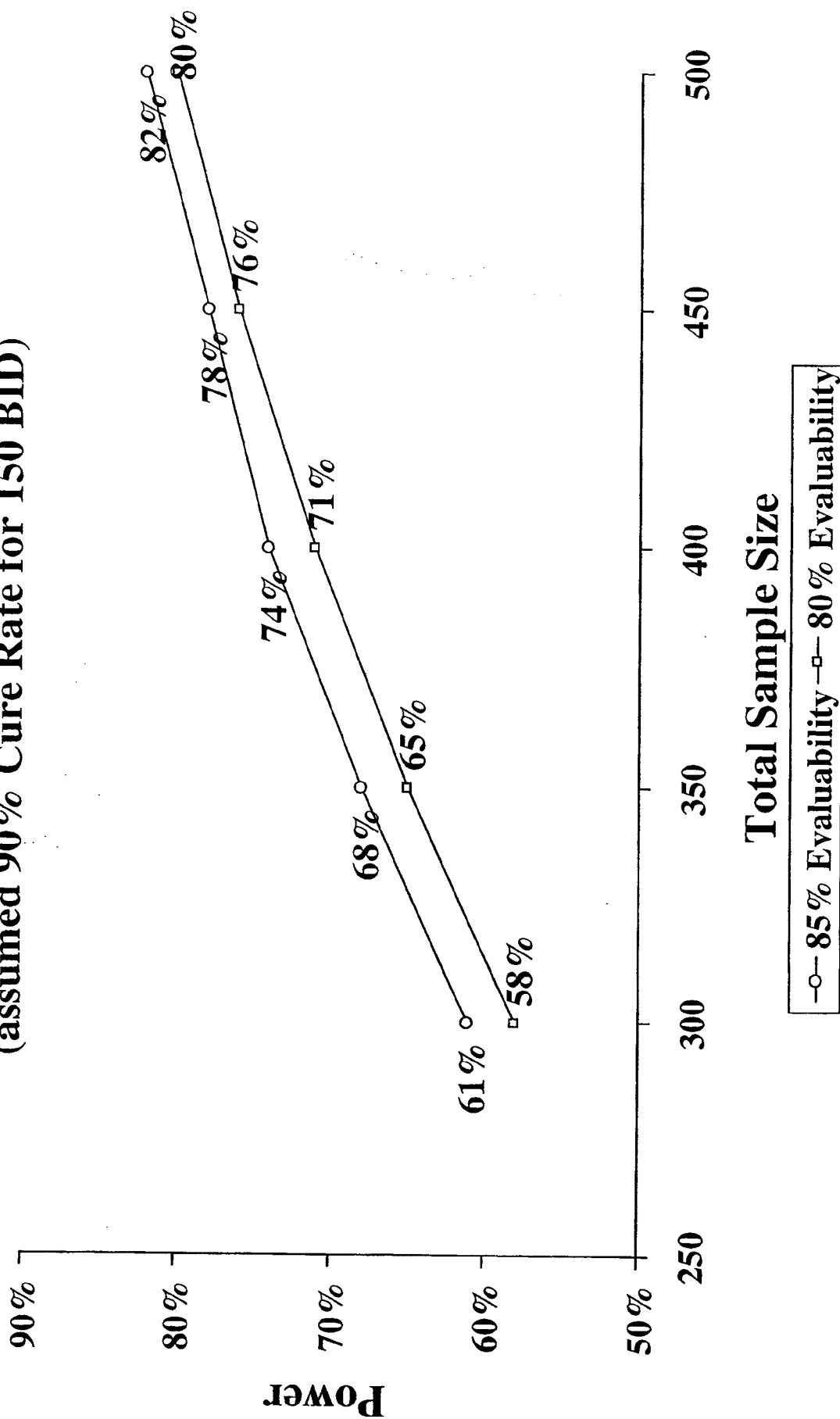
# Possibilities

- Make enrollment targets on time
- A little behind
- Way behind

# Activities-to-date to address CAP enrollment

- Increased European sites from 79 to 130 in Nov. 2000
- Site approvals expedited
  - Amendments translated and submitted to Ethics Committees for 350 sites in 1 month
  - CRO actively encouraging investigators to expedite EC approval process as much as possible
- Increased investigator fees
- Increased site follow up/communication
- Diligent CRO management

# **Power to Detect 10% Difference** **(assumed 90% Cure Rate for 150 BID)**



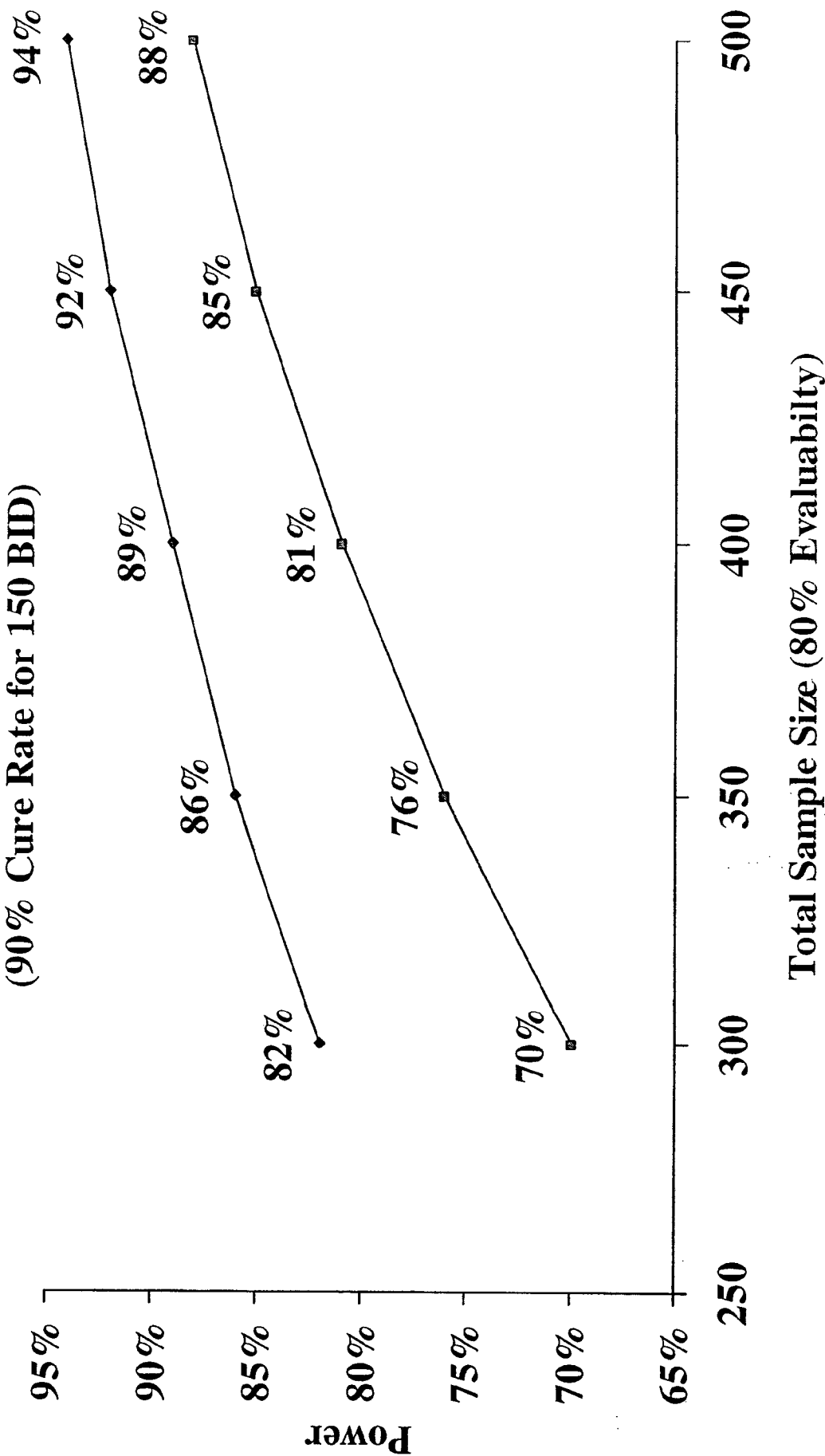


# Statistical power is a function of:

- Sample size
- Treatment arm differences
- Level of statistical significance

# Power to Detect 10 % Difference

(90 % Cure Rate for 150 BID)



—■— one-sided 10 % significance level —◆— one-sided 5 % significance level

# Possible outcomes of dose-ranging studies

**QD is:**

CAP	Sinusitis	Decision
Worse	Worse	BID
Same	Worse	BID
Worse	Same	BID or BID/QD
Same	Same	QD

# Agenda

- Market and trends
- Molecule
- Microbiology
- Pharm/tox
  - QT prolongation
  - Hepatotoxicity
- Clinical development
  - Phase I/II summary
  - Dose selection
  - Phase III program
  - Contingency plans
- Timeline and budget
- IV formulation
- Summary of key issues and action plans

# ABT-773 IV Formulation

## Strategic, Commercial, and Technical Value

- **Strategic Value**

- IV represents a channel not currently served by Anti-infective Franchise
- Leverages presence of MCRs and experience with ID community

- **Commercial Value**

- IV availability improves formulary access to molecule
  - Potential advantage over telithromycin, which will not have an IV
  - Would be competitive with Zithromax, Tequin, Avelox which have IV
- Positive impact on tablet formulation
  - estimated \$36MM incremental to peak tablet sales due to step-down therapy
  - Enhances overall “potency” image of brand

- **Technical Value**

- Support for *S. pneumoniae* Resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provides additional information on QT effects

# ABT-773 IV

## Planned Clinical Program

• Single Dose-rising Phase I study	May/01
• Multiple Dose Phase I with selected dose	Aug/01
• File US IND	Nov/01
• Initiate Phase III	Jan/02
– 2 step-down CAP studies (US/Europe)	
– 2-3 days dosing	
– Two seasons to complete	
• Filing	Dec/03

- IV launch currently lags tablet launch by 1 year
- further delays will reduce the potential value

## IV Development Cost

	Thru 2000	2001	2002	2003 to NDA	Total
Clinical Program	0.2	4.0	6.0	2.5	12.7
Phase I Single Rising Dose		0.5			0.5
Phase I Multiple Dose		0.4			0.4
Phase III 2 step-down CAP Studies (US/Europe)		2.9	6.0	2.5	11.4
CMC	1.0	2.5	1.8	1.3	6.6
Drug Safety/Other	1.0	1.0	1.0	1.0	4.0
Total by Year	2.2	7.5	8.8	4.8	23.3

# Summary: Key Issues

- **QT Prolongation**
  - Possible class labeling, with resulting safety perception
- **Resistance claim**
  - Key differentiating feature
  - Bacteremic isolates requested by FDA requires IV
- **IV Formulation**
  - Strengthens strategic, commercial, and technical value of product
- **QD vs BID dosing**
  - Divergence regulatory and commercial considerations in US vs Europe
- **Delayed Phase III program**
  - Delayed dose selection decision beyond July/Aug 2001 could delay filing

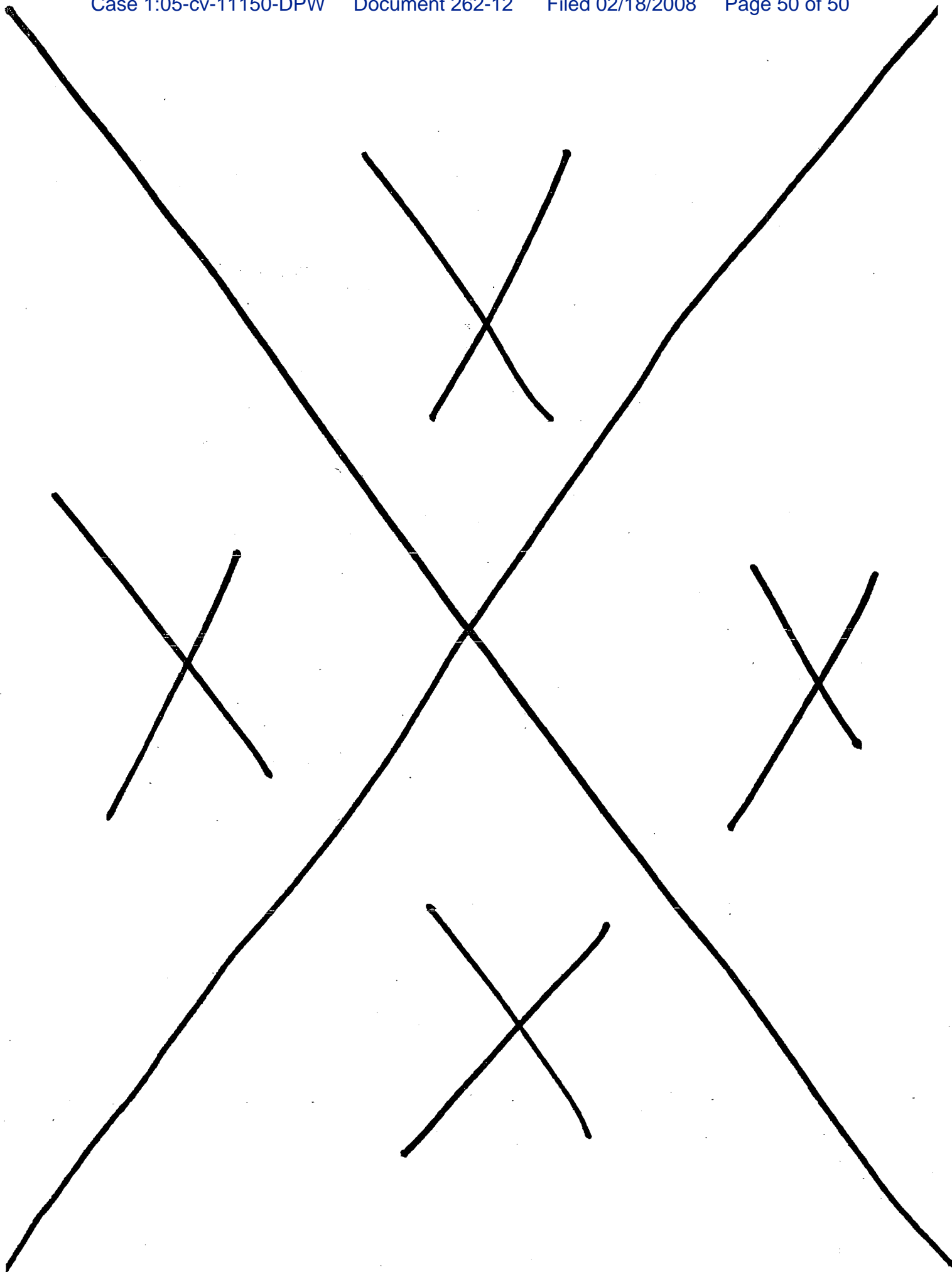


# ABT-773 Action Plans

Key Issue	Action Plans
<b>QT Prolongation</b>	<ul style="list-style-type: none"> <li>▪ Conduct EKG monitoring in Phase III to gather additional data on QT prolongation</li> <li>▪ Anticipate and fulfill regulatory expectations for animal and human data</li> </ul>
<b>Resistance claim</b>	<ul style="list-style-type: none"> <li>▪ Accrue sufficient patients to obtain necessary organisms</li> <li>▪ IV formulation would access bacteremic patients</li> </ul>
<b>IV Formulation</b>	<ul style="list-style-type: none"> <li>▪ Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding</li> </ul>

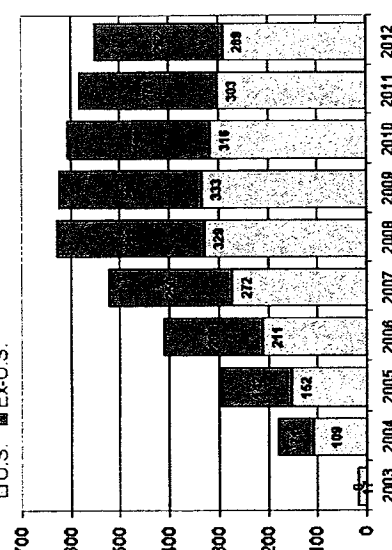
# ABT-773 Action Plans

Key Issue	Action Plans
QD vs BID dosing	<ul style="list-style-type: none"><li>▪ Select dose based on outcome of current QD vs BID trials</li><li>▪ Minimize regulatory risk</li><li>▪ Optimize global commercial opportunity</li></ul>
Delayed Phase III program	<ul style="list-style-type: none"><li>▪ CAP Study sites increased in the US and Europe from 209 to 300 sites</li><li>▪ Southern hemisphere contingency</li><li>▪ Re-evaluate other contingency plans</li></ul>





May-01										ABT-773 Ketolide Antibiotic - Tablet										Indication(s)													
Franchise		Dev. Status		Brand Name		Generic Name		Patent Exp.		2017										Bronchitis, pharyngitis/sinusitis, community-acquired pneumonia, sinusitis													
Anti-Infective		Phase III		Under Development		Pending																											
● ABT-773 is a potent antibiotic that has excellent activity against respiratory pathogens, including penicillin/macrolide resistant <i>S. pneumoniae</i>														● ABT-773 will be dosed QD for 5 days for AECB and pharyngitis; dosing for CAP and sinusitis will be either 150 mg QD or 150 mg BID for 10 days				● ABT-773 will compete with macrolides on the basis of superior activity against resistant organisms (resistance claim being pursued) and improved mechanism and against quinolones on the basis of appropriate use, efficacy, and safety															
Unit		Value		%96-00		Unmet Need/Key Market Drivers										Key Competitors/Position to Market																	
TRX		217 MM		0.7%		Unmet need in community RTI is relatively low. Key market drivers are resistance (ability to treat resistant organisms along with low propensity to develop resistance), tolerability, and convenience. A single agent that can offer relatively high levels of efficacy/resistance coverage, tolerability/safety, and convenience would be expected to gain market acceptance. A number of key antibiotics lose patent exclusivity in 2003-2005 (Biaxin, Zithromax, Levaquin, Cipro), which may negatively impact future prices.										Key competitors are other macrolides (Zithromax), quinolones (Levaquin, Tequin, Avelex), Augmentin and cephalosporins (numerous). Aventis filed an NDA for their ketolide Ketek (telithromycin) 300; approved by CPMP but FDA advisory recommended only CAP for approval citing safety concerns and lack of data in resistant isolates.																	
TRX		1,290 MM		0.4%		Need exists for agents active against pen and macrolide resistant pathogens, without the safety concerns currently associated with the quinolone class. Pharmacoeconomic issues are of increasing concern to government-controlled healthcare systems, leading to higher hurdles for regulatory approval regarding therapeutic benefit vs. existing therapies, strict price/reimbursement controls, and push for shorter courses of therapy.										Augmentin and cephalosporins dominate most AI markets; quinolones dominate in Japan, with cephs a close second. New quinolones (levo, moxi gal) recently launched ex-Japan; however, current use is predominantly in more severe infections (e.g. CAP) due to safety concerns and premium pricing vs. other agents. Aventis ketolide (Ketek) expected to launch Q2 2001 with inferior tolerability profile vs. ABT-773.																	
Sales		\$6,867 MM		-1.5%																													
Cost to NDA		DDC Est.		Thru 2000		2001		YTD		Proj.		Budget		Var		2002		2003		2004		2005		2006		Post LRP		Total		Development Timeline			
Clinicals		NA		\$35.9		\$61.2		\$60.7		-\$0.5		\$39.9		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$137.0		Start of Tox Phase I		Mar-97		Jun-97	
CMC		NA		\$77.3		\$20.2		\$20.2		\$0.0		\$14.5		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$112.0		Phase II		Oct-97		Dec-97	
Drug Safety		NA		\$0.8		\$2.1		\$2.1		\$0.0		\$1.0		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$11.9		Phase III		Dec-98		Sep-99	
Other		NA		\$31.3		\$1.4		\$5.0		\$0.0		\$5.9		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$42.2		Last Pt/Last Visit		Jun-00		Nov-00	
TOTAL		\$200.0		\$153.3		\$41.9		\$88.5		-\$0.5		\$61.3		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$0.0		\$303.1		US: EU, Japan Filing		Dec-00/Dec-00/TBD		Aug-02/Aug-02/TBD	
Projected Actual of \$88.5MM includes IV Single dose study (\$5MM).																												US: EU, Japan Approval		Dec-01/Dec-01/TBD		Aug-03/Aug-03/TBD	
Base Case Forecast (to be revised in light of ongoing DSG analysis)																																	
Base Case Assumptions (to be revised in light of ongoing DSG analysis)																																	
Product Profile (Efficacy, Safety, Convenience)																																	
Efficacy: Comparable cure/radiation rates (80-90%) vs comparators																																	
Efficacy: No resistance claim, but in-vitro data is available																																	
Safety/AE: Adverse events comparable to Biaxin XL																																	
Safety/AE: No major safety issues/product-specific labelling																																	
Conven. 150 mg QD dosing for AECB & pharyngitis																																	
Conven. 150 mg QD or BID dosing for CAP & sinusitis																																	
Conven. AECB & pharyngitis: 5-day dosing																																	
Conven. CAP & sinusitis: 10-day dosing																																	
Taste: 5%																																	
Nausea: 5%																																	
Diarrhea: 5-10%																																	
Prob: Medium																																	
Share Impact: High																																	
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**May 2001****ABT-773****Monthly Highlights – Key Project Progress**

- Phase IIIa enrollment for CAP (295 actual) and ABS (406 actual) are behind projections to support a dose decision in June. A decision analysis process has been ongoing to evaluate Phase IIIb study options, and will make a recommendation in June.
- Phase III sites in Central America for CAP and ABS, and in So Africa and So America for CAP, are currently being initiated to enroll during their winter seasons to achieve the necessary enrollment targets.
- A strategy to address European and US requirements regarding QT intervals has been implemented. A retrospective review of appropriate EKG of completed studies ongoing, along with additional review of EKGs obtained the current Phase III studies. An expert assessment of these data will provide further support for proceeding in Phase III. In addition, a Phase I QT study is being initiated to start in the July/August timeframe dependant on FDA approval.
- Meeting with Opinion leader re LFT issue undertaken and reassurance given on current data. Further data needed in respect of Japanese patients.
- The initial Phase I study for the IV formulation will start in August to evaluate dose levels, concentration and rates of infusion. Based on positive results and a Go decision, we plan to do further Phase I evaluation by the end of 2001 and start Phase III in mid-2002. An IV formulation will provide further support for the tablet filing.
- An assessment of the Pediatric development to-date was completed, and a proposal to move forward with further formulation development and Phase I studies is being developed. FDA guidelines for a pediatric formulation require companies to show due diligence with a pediatric development program. A pediatric proposal will be made to senior management.

**Next Quarter's Key Progress Markers**

Key Progress Marker	Target Date
Complete decision analysis process to determine Dose selection strategy and Phase IIIb comparator study options to present management recommendation.	06/15
Complete retrospective review of EKGs obtained from Phase I and II studies.	06/30
Initiate Phase I QT study.	07/31
Initiate first Phase I study of IV formulation.	08/27
Discuss Japanese program strategy with Daiinabot and Taisho to evaluate impact of results of Japan Phase I studies and to define strategy for Phase IV/III study plans.	06/26
Finalize plans for a pediatric formulation development program.	07/31

**Key Project Issues and Risks**

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
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**May 2001****ABT-773****Key Project Issues and Risks**

<b>Risk or Issue</b>	<b>Potential or Known Impact</b> Check all that apply and Describe Impact <u>X</u> Cost <u>X</u> Time <u>  </u> Profile <u>  </u> Regulatory Critical path trials to development timeline are CAP & sinusitis, with dose decision for these indications needed by 7/2001 to maintain current timeline. Actual enrollment is lagging predictions.	<b>Strategy / Progress</b>	<b>Area / Responsibility</b>	<b>Resolution Date</b> Planned / Actual
Clinical enrollment challenges due to a) delay in end of phase II meeting from September to November at request of FDA b) delay in start of study due to protocol changes requested by FDA c) light 2000-01 flu/respiratory season	<u>X</u> Cost <u>  </u> Time <u>  </u> Profile <u>  </u> Regulatory Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing would result in a negative commercial impact.	A decision to initiate the Southern Hemisphere sites was made in April to continue enrollment for CAP and sinusitis. ASP and ABECB studies are not on the critical path but will take longer than planned to complete enrollment.	Venture	7/2001
150 mg QD vs BID dose decision in CAP/sinusitis.	<u>X</u> Cost <u>  </u> Time <u>  </u> Profile <u>  </u> Regulatory Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing would result in a negative commercial impact.	Ongoing DSG will consider dose issue, recommendation planned mid-June. Phase IIb comparator study plans to take into consideration input gained from the recent Ketek FDA advisory in April	Venture/NPD/DSG	7/2001
Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	<u>  </u> Cost <u>  </u> Time <u>  </u> Profile <u>  </u> Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product.	<b>Acute tox study in conscious dog showed no difference from the earlier sedated dog study. A QT strategy has been implemented in light of the cardiology advisory held May 14<sup>th</sup>. Retrospective analysis of all EKGs obtained to-date is ongoing and the Phase I QT study is planned to initiated as soon as possible in July 2001.</b>	Regulatory	6/2002
Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch.	<u>X</u> Cost <u>  </u> Time <u>  </u> Profile <u>  </u> Regulatory Ability to define step 5 as the starting material will allow us to make further process improvements to reduce the cost of the bulk drug.	The end of Phase II package outlining our plans for starting materials was presented to FDA at the End of Ph II meeting held with FDA on May 1st. We received support from FDA for our approach in defining the PQ Ery A dibenzoate (step 5 intermediate) as the starting material. We will follow up on their additional comments.	SPD	04 2001/ 05 2001

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May 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact ___ Cost ___ Time ___ X ___ Profile ___ Regulatory Support by PK/PD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model.	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially, particularly with respect to <i>H. influenzae</i> .		PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. DSG analysis is addressing dose issue. To address this issue and potentially create a new model for evaluating PK/PD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study.	Venture/NPD	07/2001
Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .	___ Cost ___ Time ___ X ___ Profile ___ Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim.	FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. The Ketek FDA experience indicates that number of isolates, clinical success, and patient severity all figure into their decision. The DSG analysis is evaluating strategies to increase the likelihood of gaining the claim, such as increased patient numbers and the impact of an IV program to target severe/bacteremic patients. A Phase I study to evaluate the IV formulation prototype will initiate in August 2001.	Venture	06/2002
Phase I was repeated in Japan to further evaluate dose-ranging. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	___ Cost ___ Time ___ X ___ Profile ___ Regulatory	The Japan Phase I Dose-Ranging study results showed no difference between Japanese and Caucasians subjects and did not show liver elevations as seen in the Hawaii study. The Japan program is being re-evaluated in light of the dose decision timeframe and Taisho/Dainabot proposed program changes. Follow up discussions are scheduled.	Japan	08/2001/

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**May 2001****ABT-773****Key Project Issues and Risks**

<b>Risk or Issue</b>	<b>Potential or Known Impact</b> Check all that apply and Describe Impact <input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding.	<b>Strategy / Progress</b>	<b>Area / Responsibility</b>	<b>Resolution Date</b> Planned / Actual
The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed.		The single-rising dose Phase I study protocol has been amended to incorporate changes to doses, concentrations used and infusion times to allow for additional evaluation of QT effects within this study. This will delay the start of the study to August and also allow time to assess the results of the IV studies being conducted in dog. A Go/No go decision on the IV formulation can be made once results of the Phase I study are available (October 2001).	HPD, Venture	09/2001
In light of the Ketec advisory focus on hepatic toxicity an a similar analysis of liver function tests has been undertaken for ABT 773	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	A benchmark comparison to Clarithromycin as well as Ketec data is being undertaken. Visit to Univ of Texas opinion leader undertaken. Current data in his opinion will not adversely affect approvability. Ongoing safety reviews of LFT data planned at appropriate intervals.	Venture	05/31

**May 2001****ABT-773****Key Activities**

Commercial		
Activity	LBE	Actual
Completion of study tracking intranet	2Q01	
Integration of intranet into communication plan	2Q01	
Integration of intranet into draft product label	2Q01	
Identification of communication vendor	3Q01	
Submission of brand/USAN names	2Q01	USAN submitted 3/01, cetirizine & loratadine accepted; brand to be submitted 6/01
Preliminary qualitative positioning research	4Q01	
Quantitative market research to support revised forecast	4Q01	
Preliminary qualitative positioning research	4Q01	

Formulation		
Activity	Plan	Actual
Phase I Formulation (Caps)*	12/1997	12/1997
Phase II Formulation (Tablet)	7/1999	8/1999
Clinical Supplies Phase IIB	7/1999	8/1999
Phase III Formulation (Tablet)	4/2000	7/2000
Phase III Clinical Supplies Manufactured	9/2000	9/2000
NDA Lots (3) Completed	7/2000	01/2001
Completion of 1 Year Stability for NDA	8/2001	
Formulation Peer Review	11/2001	

Drug Substance		
Activity	KG	Plan
Actual	Actual	Actual Projected Cost/kg

Toxicology		
Plan Start ??Date??	Actual Start Date	Report Completed
2-week oral Rat/Monkey	7/1997	6/1997
Acute Studies	8/1997	8/1997
Mouse Lymphoma/Micronucleus	11/1997	11/1997
1 Month Rat/Monkey	12/1997	12/1997
Pregnant Rat/Rabbit RF	1/1998	1/1998
SEG II Rat/Rabbit	3/1998	3/1998
Guinea pig sensitization	11/1998	11/1998
3 Month oral Rat/Monkey	9/1999	10/8/1999
Seg I/III Rat	9/1999	10/8/1999
IV Irritation studies, set 1	7/1999	7/15/1999
IV Irritation studies, set 2	2/2000	2/2000
IV 2-week Rat/Monkey Studies	6/2000	6/2000
Neonatal/Juvenile Rat	10/1999	11/1999

\* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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May 2001

ABT-773

## SPD ABT-773 Bulk Drug Deliveries Update

	Target Date	Amount	Delivery Date	Amount	Lot #	Amount after milling
Campaign 1	2/28/99	200 Kg	2/23/99	209 Kg	50-007-CA-00	207.5 Kg (2/26)*
Campaign 2a	6/15/99	140 Kg	6/17/99	131 Kg	54-702-NI-00	129.4 Kg (6/19)*
Campaign 2b	7/15/99	140 Kg	7/21/99	121.5 Kg	55-208-CB-00	119.3 Kg (8/4)*
Tox lot	8/30/99	5 Kg	8/25/99	6.1 Kg	55-718-NI-00	
Campaign 3a	9/30/99	160 Kg	10/8/99	170.5 Kg	58493CB00	138.4 Kg (10/16)*
Campaign 3b	10/21/99	160 Kg	10/11/99	176.5 Kg	58494CB00	169.5 Kg (10/16)*
Pilot run 1	-----	15 Kg	10/30/99	18.9 Kg	59763N100	no milling
Pilot run 2	-----	15 Kg	2/5/00	15.5 Kg	61790NI00	no milling
Pilot run 3	-----	25 Kg	1/30/00	27.5 Kg	62764CB00	27.3 Kg (4/18)*
Campaign 4	12/10/99	320 Kg	11/23/99	355 Kg	61741CB00	309 Kg (3/2)*
Campaign 5	12/30/99	300 kg	12/16/99	300.5 Kg	60665CB00	269.2 Kg (3/3)*
Campaign 6	2/28/00	280 Kg	2/23/00	321 Kg	62796CB00	315.5 Kg (3/6)*
Campaign 6 (IV)	2/28/00	15 Kg	2/22/00	20 Kg	62797CB00	18 Kg (3/15)*
Campaign 7	3/30/00	300 Kg	4/10/00	370 Kg	63890CB00	361.2 Kg (4/18)*
Campaign 7 (IV)	3/30/00	5 Kg	3/29/00	19 Kg	63889CB00	17.2 Kg (4/11)*
Campaign 8	4/25/00	200 Kg	5/11/00	263 Kg	64970CB00	256.5 Kg (5/15)
Campaign 8 (IV)	4/25/00	15 Kg	4/25/00	19.8 Kg	64971CB00	17.7 Kg (5/11)*
Campaign 9	6/15/00	300 Kg	6/14/00	375.7 Kg	65064CB00	355.7 Kg (6/20/00)
Campaign 9 (IV)	6/15/00	15 Kg	6/5/00	18.1 Kg	65065CB00	16.7 Kg (6/9/00)*
Campaign 10	7/15/00	300 Kg	7/26/00	361.2 Kg	67176CB00	359.0 Kg (8/10/00)
Campaign 11	8/15/00	300 Kg	8/4/00	333.7 Kg	68285CB00	271.9 Kg (9/7/00)
Campaign 12	10/6/00	300 Kg	9/27/00	356 Kg	69458CB00	292.3 Kg (12/8/00)
Campaign 13	11/23/00	300 Kg	11/15/00	351.2 Kg	71665CB00	349.1 Kg (12/20/00)
Total (year 2000)						2,815.5 Kg
Campaign 14	1/28/01	300 Kg	1/26/01	327.5 Kg	73886CB00	318.9 Kg(02/13/01)
Campaign 15	2/10/01	330 Kg	1/14/01	354.9 Kg	71699CB00	353.8 Kg(02/02/01)
* Weight after rework						

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**May 2001****ABT-773****All Clinical Studies:**

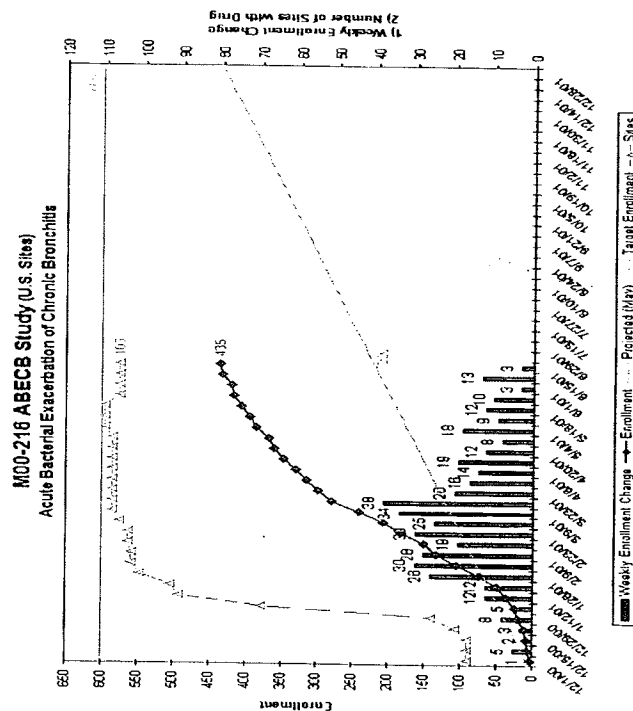
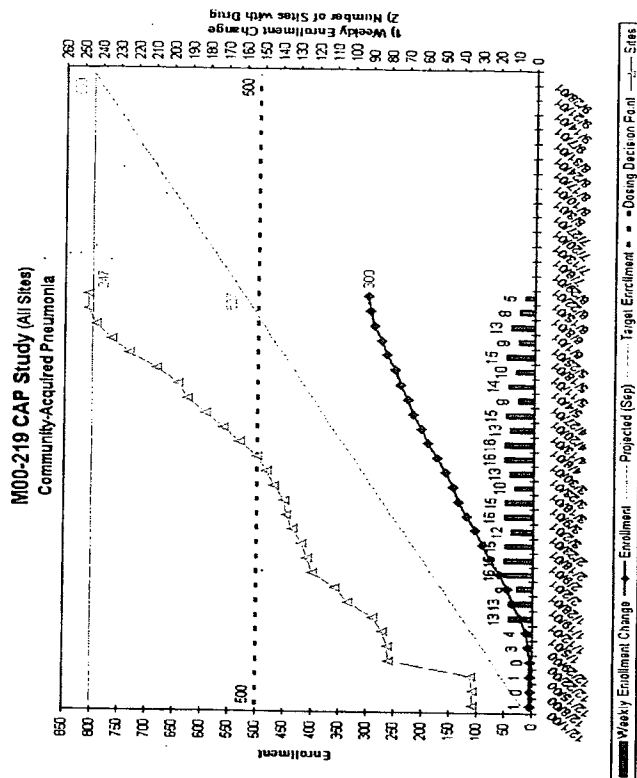
Protocol Number	Phase	Study Name	Start 1 <sup>st</sup> Pt. Dosed	End (Last CRF In)	Patients		Protocol Number	Phase	Study Name	Start 1 <sup>st</sup> Pt. Dosed	End (Last CRF In)	Patients	
					Target	Current						Target	Current
M99-048	II	Dose Ranging, ABECB	9/1/99	3/31/00	300	384							
M99-053	II	Dose Ranging, Sinusitis	9/1/99	4/30/00	300	292							
M99-054	II	Dose Ranging CAP	9/1/99	4/30/00	300	187							
M00-219	III	CAP, Dose Ranging	11/7/00	12/31/01	800	295							
M00-216	III	ABECB vs Azithromycin	11/7/00	12/31/01	600	422							
M00-217	III	ABECB vs Levofloxacin	11/7/00	12/31/01	500	123							
M00-225	III	Sinusitis Dose Ranging	11/7/00	12/31/01	600	406							
M00-223	III	Pharyngitis vs Penicillin 500mg TID	11/7/00	6/30/01	520	503							
M00-222	III	Pharyngitis vs Penicillin 500mg TID	11/7/00	12/31/01	520	37							
M01-325	I	QT Phase I Study	08/01	10/30/01	68								

May 2001

ABT-773

# Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol:	M00-219 -- Dose-Ranging CAP	M00-216 -- Phase III ABECB vs Azithromycin
Objective:	Dose selection.	Safety & Efficacy
ABT-773 Doses:	150mg QD vs 150mg BID, 10 days	150mg QD, 5 days
Comparator Doses:	None	Azithromycin 500mg day 1, 250mg QD for 4 days
Target Enrollment:	800	600
Status:	Currently enrolling	Currently Enrolling
Major Findings:		



Author:  
(Double click on chart to edit)

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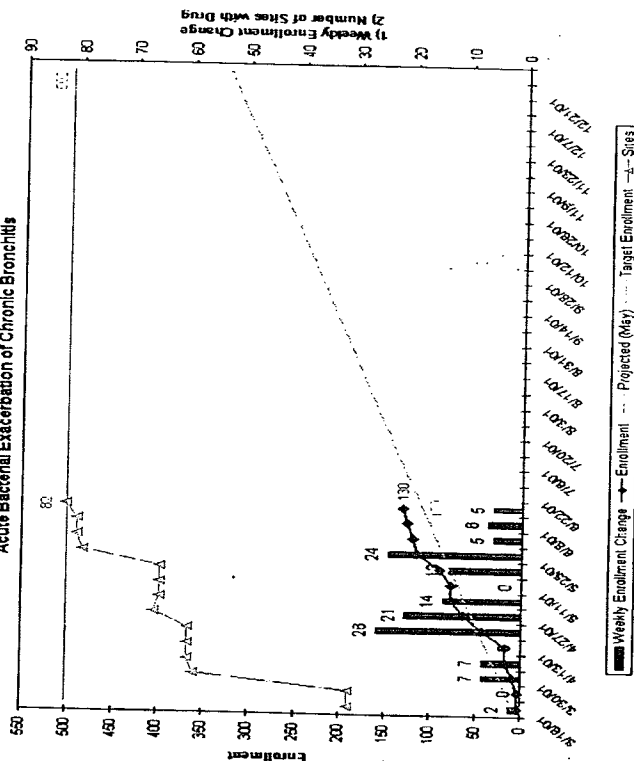
ABT-773

# Ongoing Clinical Studies

(List first time in man, Phase II Dose-Ranging and Pivotal Trials)

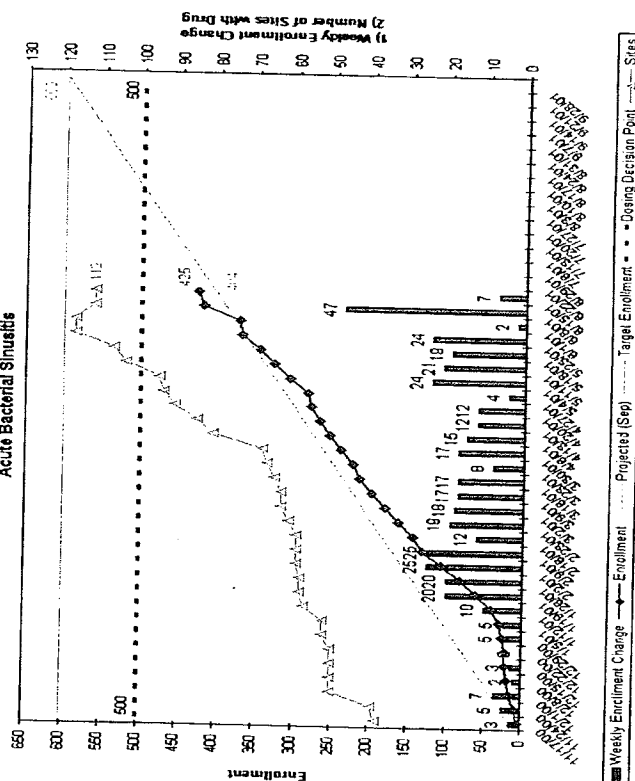
Protocol:	M00-217 - Phase III ABECB vs Levofloxacin	M00-225 - Sinusitis Dose-Ranging
Objective:	Safety & Efficacy	Dose Selection
ABT-773 Doses:	150 mg QD	150mg QD vs 150mg BID, 10 days
Comparator Doses:	Levofloxacin 500mg QD for 7 days	None
Target Enrollment:	500	600
Status:	Currently enrolling	Currently enrolling
Major Findings:		

M00-217 ABECB Study (Ex-U.S. Sites)  
Acute Bacterial Exacerbation of Chronic Bronchitis



Author:  
(Double click on chart to edit)

M00-225 ABS Study (All Sites)  
Acute Bacterial Sinusitis



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ABT-773

Ongoing Clinical Studies

(List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol:

M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID

Objective:

Safety & Efficacy

ABT-773 Doses:

150mg QD., 5days

Comparator Doses:

Penicillin 500 mg TID, 10 days

Target Enrollment:

520

Status:

Currently enrolling

Major Findings:

M00-222 – Phase III Pharyngitis vs Penicillin 500mg TID

Safety & Efficacy

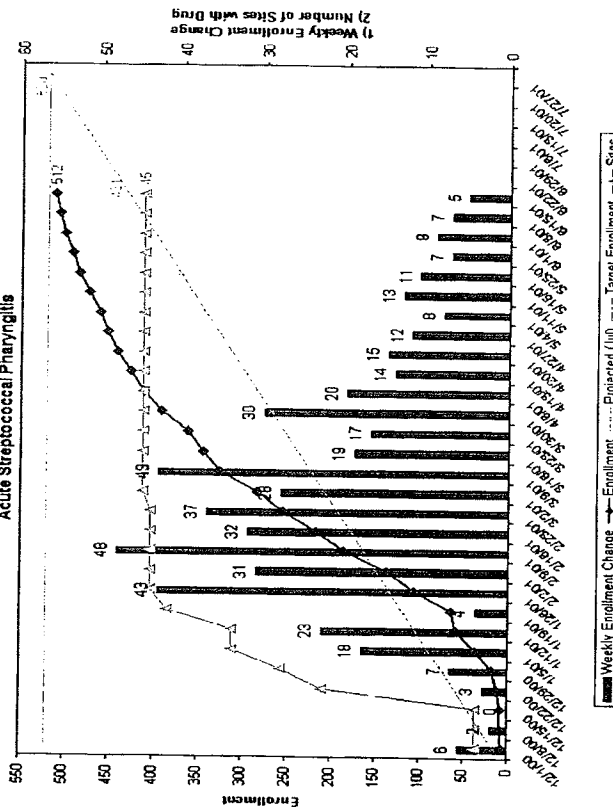
150mg QD, 5 days

Penicillin 500mg TID, 10 days

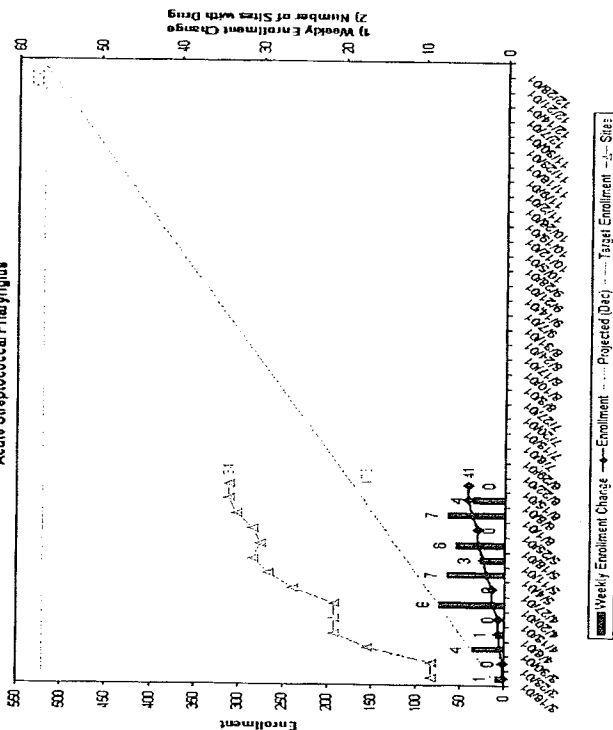
520

Currently enrolling

M00-223 ASP Study (U.S. Sites)  
Acute Streptococcal Pharyngitis



M00-222 ASP Study (Ex-U.S. Sites)  
Acute Streptococcal Pharyngitis



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ABT-773

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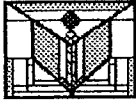
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Carol S  
Meyer/LAKE/PPRD/ABBOTT  
06/20/2001 05:52 PM

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cc s09376@ccm.taisho.co.jp, s10599@ccm.taisho.co.jp,  
s13161@ccm.rd.taisho.co.jp, s13221@ccm.taisho.co.jp,  
s13503@ccm.taisho.co.jp, s14279@ccm.rd.taisho.co.jp,  
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bcc

Subject Re: Re[2]: ABT 773 Taisho/Abbott Meeting, June 26th

Dear Mr. Nakajima,

Thank you for your feedback regarding the draft agenda for next week's meeting, we accept the changes you propose. Once you have had the opportunity to meet with Mr. Kuzuhara at Dainabot, please let me know of any additional revisions. We will make every effort to be prepared to answer all of your questions, and look forward to a very productive meeting

I have also collected the second package of information to send for your review prior to the meeting and have attached it below. Please let me know if there is anything else you would like to me send, and I will do my best to get it to you. We plan to have further detail to present at the meeting regarding the dose decision rationale, it is not currently available to send with this package.

Thank you for all of your support and I'm looking forward to meeting with you

Best regards,

Carol



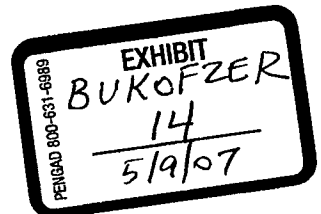
Dose Decision rationale 6.14.01 Taisho mtg.ppt



ABT 773 Clinical Status Taisho.ppt



Phase3SAEs.ppt



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ABBT229367



773 core update 6-11.ppt

# ABT-773 Pharmacokinetic Update

Linda E. Gustavson, PhD

Section Manager

Clinical Pharmacokinetics Department

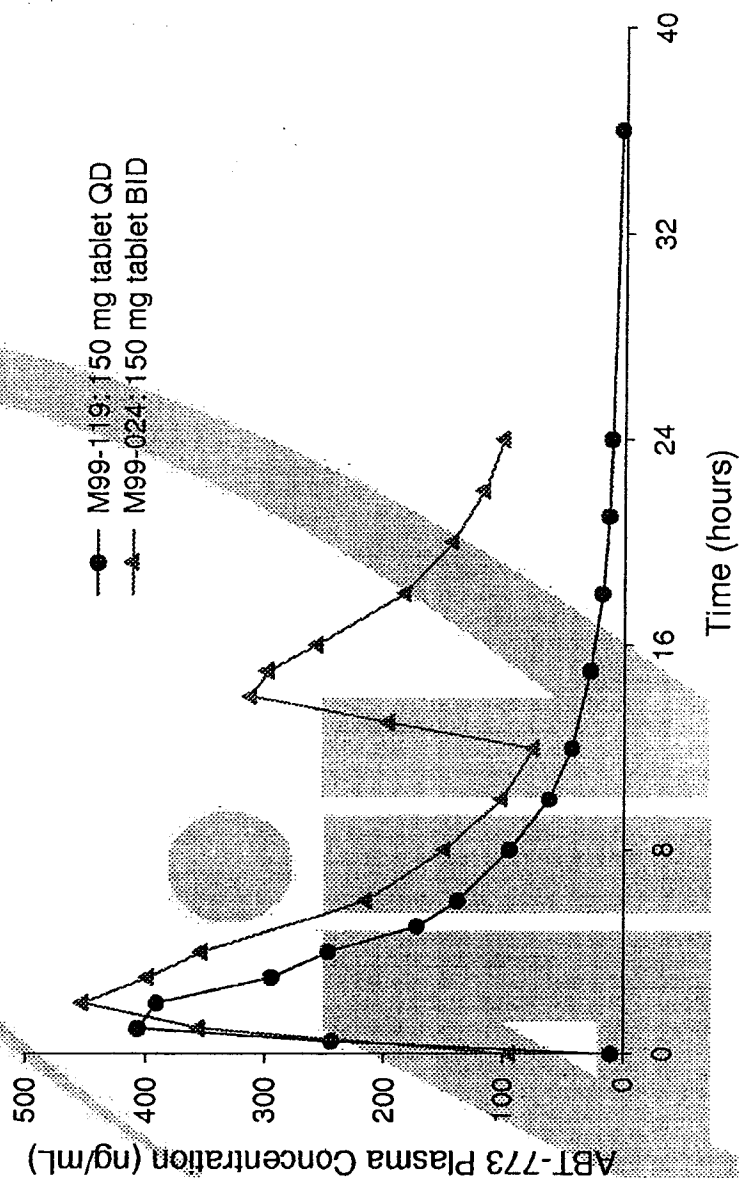
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## Characteristics of ABT-773 PK

Nonlinear PK throughout the clinically relevant dose range

- 150 mg QD, 150 mg BID, 300 mg QD
- Greater than proportional increases in exposure (AUC) with dose
- Greater exposure (AUC) is obtained with QD dosing
- Food does not significantly influence bioavailability
- High protein binding (>95%) for parent and major metabolite
- Exclusively metabolized by CYP3A
- Inhibitor of CYP3A metabolism
- Transported by Pgp
- Inhibitor of Pgp transport

# ABT-773 Plasma Concentration Profiles: 150 mg QD and 150 mg BID



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**ABT-773**  
**Pharmacokinetics:**  
**150 mg QD and 150 mg**  
**BID**

Study M99-119		Study M99-024
Pharmacokinetic Parameters	150 mg Tablet QD (N = 12)	150 mg Tablet BID (N = 18)
C <sub>max</sub> (ng/mL)	498 ± 295	580 ± 256
T <sub>max</sub> (h)	1.1 ± 0.6	2.1 ± 1.0
C <sub>min</sub> (ng/mL)	10 ± 3	71 ± 33
AUC <sub>0-24</sub> (ng·h/mL)	2347 ± 824	4997 ± 2250



## Excretion of ABT-773

- 150 mg single dose of  $^{14}\text{C}$ -labeled ABT-773
- 94% of radioactivity eliminated by 168 hours
  - 87% in feces
    - 35% N-desmethyl metabolite, 31% ABT-773,
    - Remaining 34% as small amounts of 5 other metabolites
  - 7% in urine
    - 90% ABT-773, 10% N-desmethyl metabolite



# Drug Interaction Studies: Completed

## ABT-773 as Victim - Ketoconazole

- ABT-773 is a CYP3A substrate *in vitro*
- Ketoconazole is a prototype CYP3A inhibitor
- With ketoconazole:
  - ABT-773 AUC increased about 5 times
  - ABT-773 C<sub>max</sub> increased about 2.5 times
  - Formation of N-desmethyl ABT-773 reduced

## Drug Interaction Studies: Completed

### ABT-773 as Victim - Rifampin

- ABT-773 is oxidatively metabolized
- Rifampin is a prototype inducer
- With rifampin:
  - ABT-773  $C_{max}$  and AUC decreased by >90%
  - Formation of N-desmethyl metabolite reduced by >60%

# Drug Interaction Studies: Completed

## ABT-773 as Perpetrator - Oral Contraceptive

- Likely to be co-administered
- Need to assure safety and maintain efficacy
- With ABT-773:
  - Ethinyl estradiol AUC increased by 6%
  - Norethindrone AUC increased by 30%
  - No clinically important changes in OC PK
  - Efficacy of OC not compromised

## Drug Interaction Studies: Completed

### ABT-773 as Perpetrator - Theophylline

- Likely to be co-administered (bronchitics)
- Theophylline has narrow therapeutic index
- With ABT-773:
  - Theophylline  $C_{max}$ ,  $C_{min}$  and AUC increased 12-13%
  - 90% confidence intervals meet requirements for bioequivalence
  - No clinically important changes in theophylline PK

# Drug Interaction Studies: Completed

## ABT-773 as Perpetrator - Midazolam

- ABT-773 inhibits CYP3A *in vitro*
- Midazolam is a prototype CYP3A substrate
- With ABT-773 (at 300 mg QD):
  - Midazolam  $C_{max}$  increased about 50%
  - Midazolam AUC increased 123%
  - Interaction significant but less than observed with ketoconazole, telithromycin or clarithromycin
  - Midazolam a very sensitive substrate



## Drug Interaction Studies: Ongoing

### Warfarin

- Likely to be co-administered
- Narrow therapeutic index
- R-enantiomer metabolized by CYP3A
- ABT-773 (perpetrator) may inhibit metabolism

### Digoxin

- Likely to be co-administered
- Narrow therapeutic index
- Pgp substrate
- ABT-773 (perpetrator) may inhibit transport

ABBT229380

# Special Populations

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## M99-126: Study Design

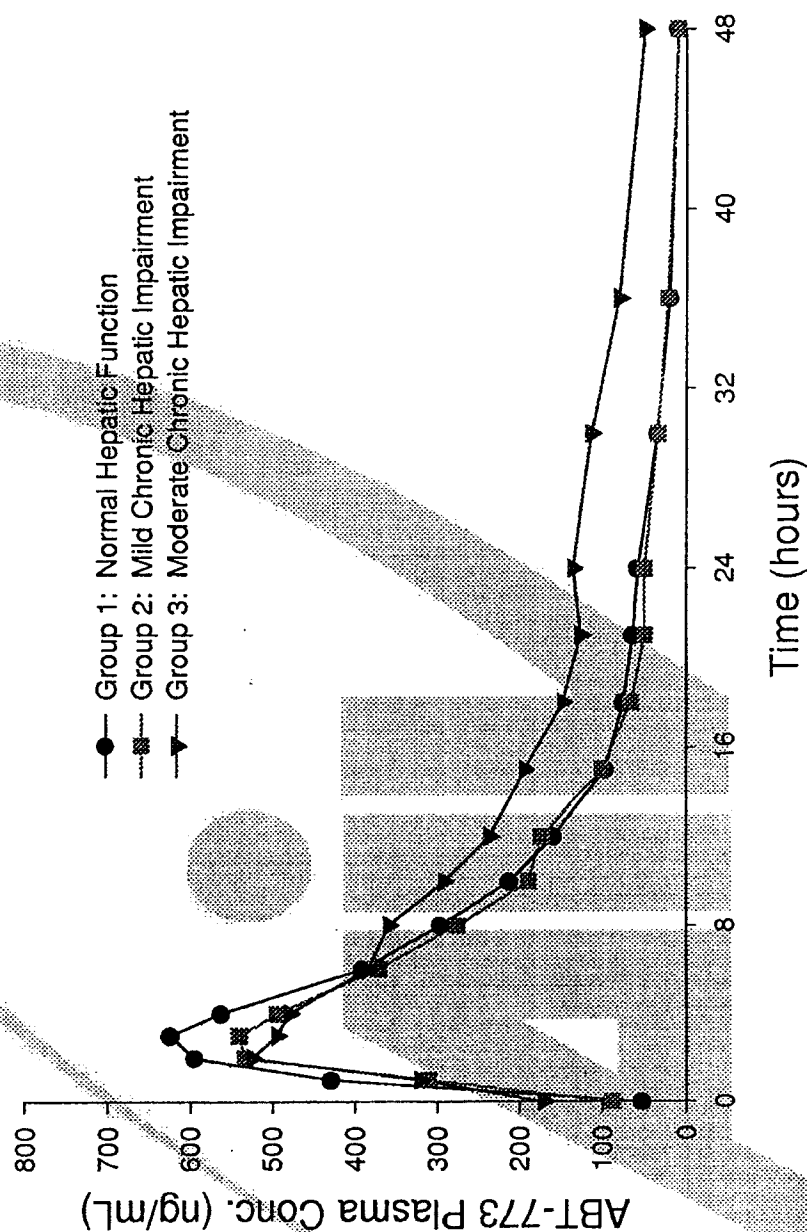
- Open-label, multiple-dose PK/safety study
- Single site (VA Medical Center, San Diego, CA)
- Three parallel groups of subjects
  - Normal hepatic function (N=12)
  - Mild hepatic impairment, Child-Pugh Class A (N=6)
  - Moderate hepatic impairment, Child-Pugh Class B (N=6)
- ABT-773 Dose: 300 mg QD x 5 days
- Serial blood samples x 48 h after last dose
- Measure ABT-773 and N-desmethyl metabolite
- Determine ABT-773 protein binding
- Complete statistical analysis (ANCOVA) planned



# PART 2

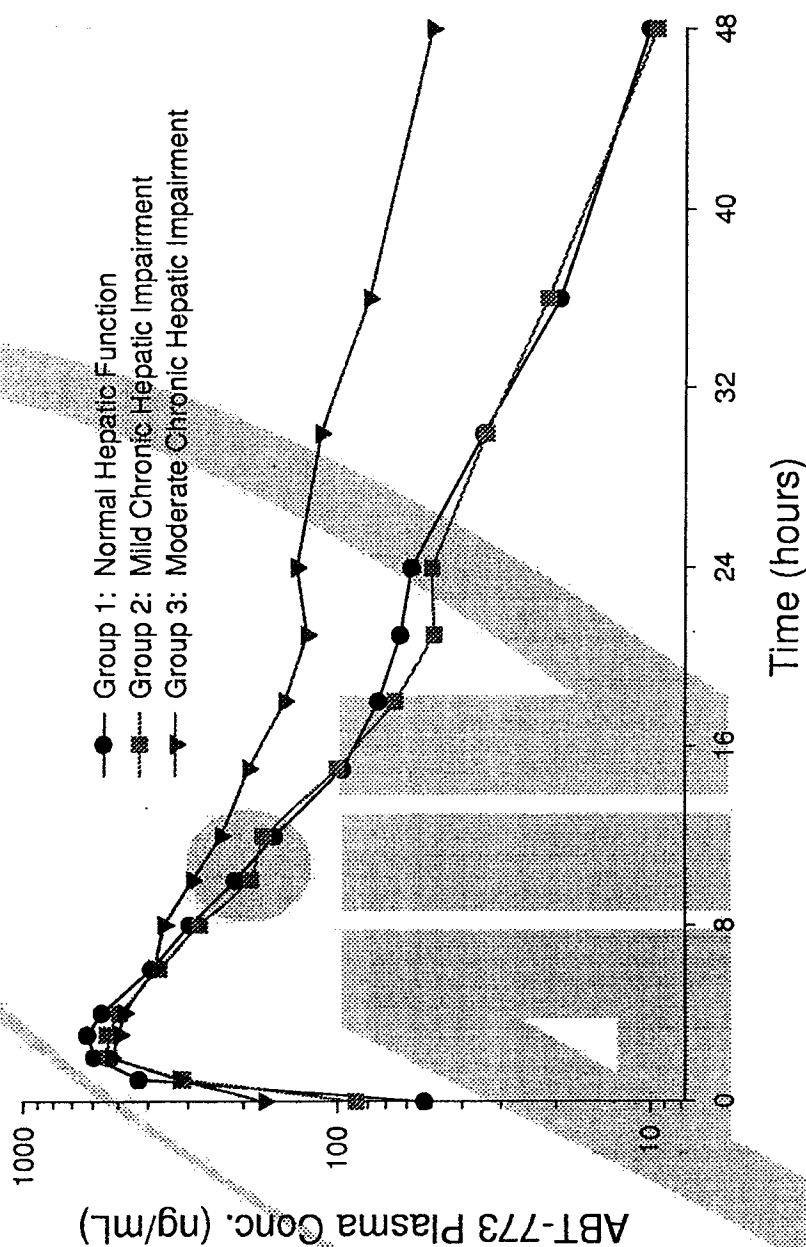
ABBT229382

# Study M99-126: Preliminary Plasma Concentration-Time Profiles



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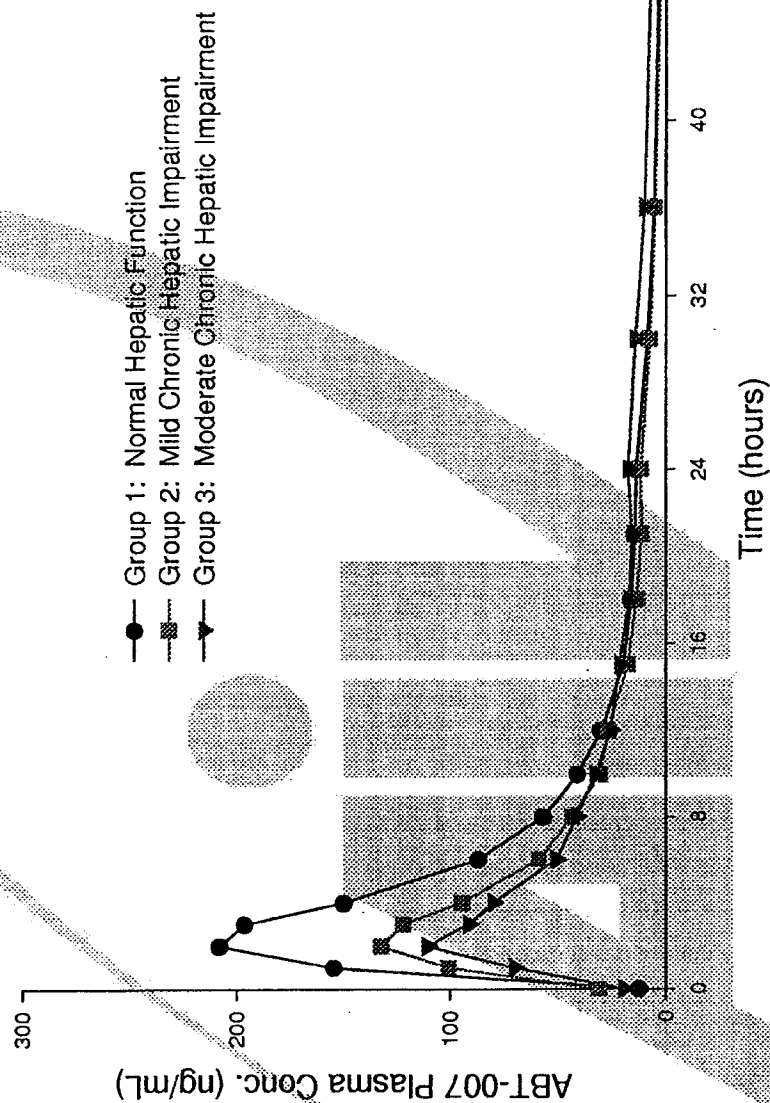
# Study M99-126: Preliminary Plasma Concentration-Time Profiles



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# Study M99-126: Preliminary Plasma Concentration-Time Profiles



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# Study M99-126: Preliminary PK Data

Group	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC <sub>24</sub> (ng·hr/mL)	t <sub>1/2</sub> (h)
Total ABT-773				
1 (Normal)	737 ± 375	2.3 ± 0.9	5512 ± 3417	10.1
2 (Mild)	630 ± 364	2.5 ± 0.8	5004 ± 3003	10.2
3 (Moderate)	597 ± 232	2.3 ± 1.0	6424 ± 3258	13.8
Total ABT-007 (N-desmethyl ABT-773)				
1 (Normal)	258 ± 75	2.1 ± 0.8	1403 ± 378	12.3
2 (Mild)	155 ± 73	1.8 ± 1.5	991 ± 470	10.3
3 (Moderate)	126 ± 61	2.0 ± 1.1	905 ± 370	18.6

Data presented as Mean ± SD, except t<sub>1/2</sub> (harmonic mean).

# Special Population Studies: Ongoing/Planned

## Renal Impairment

- Severe impairment ( $CL_{CR}$  10-29 mL/min, N = 10)
- Healthy controls ( $CL_{CR}$  > 80 mL/min, N = 10)
- Study ongoing

## Age/Gender

- Young Males (18 - 30 yr)
- Young Females (18 - 30 yr)
- Elderly Males (> 65 yr)
- Elderly Females (> 65 yr)
- Multiple dosing for 5 days
- Use highest dose planned for marketing



## Clinical PK/PD Studies: Ongoing/Planned

### BAL

- Two studies ongoing
- 150 mg QD and 150 mg BID

### WBC

- Study planned

### ECG

- Study planned

ABBT229388

# ABT-773 Clinical Update

Joaquin Valdes, M.D.

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# Phase II Clinical Program Summary

Study	Study Drug Dose/Duration	Patient Numbers/location
M99-048 Phase IIb, Double blind Acute Bacterial Exacerbation of Chronic Bronchitis	ABT-773 150, 300 or 600 mg OD Duration: 5 days	N = 384 US, Germany, France, Italy, Spain, UK, Chile
M99-053 Phase IIb, Double-blind Acute Sinusitis	ABT-773 150, 300, or 600 mg OD Duration: 10 days	N = 292 US, Finland, Greece, Chile
M99-054 Phase IIb, Double-blind Community Acquired Pneumonia	ABT-773 300 or 600 mg OD Duration: 7 days	N = 187 US, Germany, France, Italy, Spain, Poland, South Africa

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## Phase II Clinicals

Acute Bacterial Exacerbation of Chronic Bronchitis (M99-048)  
Clinical Response

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	88% (49/56)	94% (59/63)
Clin Eval	87% (98/113)	90% (105/117)	90% (101/112)
ITT	85% (104/123)	83% (107/129)	83% (106/128)

## Phase II Clinicals

Acute Bacterial Exacerbation of Chronic Bronchitis (M99-048)  
Bacteriological Response

### Clinically and Bacteriologically Evaluable

	150mg	300mg	600mg
<i>S. pneumoniae</i>	83% (10/12)	90% (9/10)	100% (13/13)
<i>M. catarrhalis</i>	80% (8/10)	92% (12/13)	91% (10/11)
<i>H. influenzae</i>	94% (17/18)	89% (17/19)	83% (19/23)
Overall	88% (35/40)	91% (38/42)	89% (42/47)

# Phase II Clinicals

Acute Bacterial Exacerbation of Chronic Bronchitis (M99-048)  
Adverse Events

## All Adverse Events

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	6% (7/126)	19% (25/129)	29% (37/129)
Diarrhea	13% (16/126)	12% (15/129)	21% (27/129)
Nausea	7% (9/126)	13% (17/129)	30% (38/129)
Vomiting	2% (3/126)	3% (4/129)	11% (14/129)
Nausea and Vomiting	0	<1% (1/129)	4% (5/129)
Abdominal Pain	4% (5/126)	4% (5/129)	4% (5/129)

## Phase II Clinicals

Community-Acquired Pneumonia (M99-054)

Clinical Response

300 mg      600 mg

Clin and Bact. Eval

92% (54/59)      82% (47/57)

Clin Eval

92% (72/78)      80% (56/70)

ITT

84% (80/95)      73% (65/89)

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## Phase II Clinicals

Community-Acquired Pneumonia (M99-054)  
Radiographic Response

### Resolution/Improvement

300 mg                      600 mg

Clin and Bact. Eval	100% (56/56)	89% (48/54)
Clin Eval	99% (73/74)	88% (57/65)
ITT	84% (80/95)	72% (64/89)

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# Phase II Clinicals

Community-Acquired Pneumonia (M99-054)

Bacteriological Response

## Clinically and Bacteriologically Evaluable

	300 mg		600 mg
<i>S. pneumoniae</i>	87% (13/15)	100%	(7/7)
<i>M. catarrhalis</i>	75% (6/8)	50%	(2/4)
<i>H. influenzae</i>	100% (9/9)	72%	(13/18)
<i>M. pneumoniae</i>	93% (13/14)	93%	(14/15)
<i>C. pneumoniae</i>	95% (19/20)	79%	(19/24)
<i>L. pneumoniae</i>	100% (3/3)	100%	(2/2)
Overall	91% (63/69)	81%	(57/70)

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# Phase II Clinicals

Community-Acquired Pneumonia (M99-054)  
Adverse Events

## All Adverse Events

600mg

300mg

GI and Taste

Taste Perversion

Diarrhea

Nausea

Vomiting

26% (24/92)

19% (17/92)

22% (20/92)

15% (14/92)

17% (16/95)

14% (13/95)

12% (11/95)

10% (9/95)

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# Phase II Clinicals

Acute Bacterial Sinusitis (M99-053)

Clinical Response

	150 mg	300 mg	600 mg
Clin Eval	89% (70/79)	83% (70/84)	71% (59/83)
ITT	82% (72/88)	80% (72/90)	67% (59/88)

# Phase II Clinicals

Sinusitis (M99-053)

Radiographic Response

## Resolution/Improvement

	150 mg	300 mg	600 mg
Clin Eval	86% (68/79)	86% (71/83)	78% (59/76)
ITT	81% (71/88)	81% (75/90)	67% (59/88)

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# Phase II Clinicals

Sinusitis (M99-053)

Bacteriological Response

## Clinically and Bacteriologically Evaluable

	150mg	300mg	600mg
<i>S. pneumoniae</i>	3/3	8/8	9/12
<i>M. catarrhalis</i>	8/9	3/4	4/4
<i>H. influenzae</i>	3/5	7/7	5/7
<i>S. aureus</i>	1/1	1/1	3/4

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## Phase II Clinicals

Sinusitis (M99-053)

Adverse Events

### All Adverse Events

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	1% (1/97)	14% (14/98)	27% (26/97)
Diarrhea	6% (6/97)	6% (6/98)	17% (16/97)
Nausea	3% (3/97)	12% (12/98)	26% (25/97)
Vomiting	1% (1/97)	6% (6/98)	17% (16/97)

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## Phase II Clinicals

Combined AECEB, CAP, & ABS Clinical Response

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

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## Phase II Clinicals

Combined AECB, CAP, & ABS Bacteriological Response

### Clinically and Bacteriologically Evaluable

	150mg			300mg	600mg
<i>S. pneumoniae</i>	87%	(13/15)	91%	(30/33)	91% (29/32)
<i>M. catarrhalis</i>	84%	(16/19)	84%	(21/25)	84% (16/19)
<i>H. influenzae</i>	87%	(20/23)	94%	(33/35)	77% (37/48)
Overall	86%	(49/57)	90%	(84/93)	83% (82/99)

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## Phase II Clinicals

Combined AECB, CAP, & ABS Adverse Events

### All Adverse Events

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	4% (8/223)	17% (55/322)	27% (87/318)
Diarrhea	10% (22/223)	11% (34/322)	19% (60/318)
Nausea	5% (12/223)	12% (40/322)	26% (83/318)
Vomiting	2% (4/223)	6% (19/322)	14% (44/318)

# Phase II Clinicals

## Macrolide-Resistant *S. pneumoniae* Outcomes

	Resistance Mechanism	ABT-773 MIC	Bacteriologic/Clinical Outcome
<b>CAP</b>			
300 mg	1 mef/US	0.06	1 Eradication/Cure
600 mg	1 mef/US	0.12	1 Eradication/Cure
<b>SINUSITIS</b>			
300 mg	2 mef/US, 1 erm/Greece	0.06-4.0	Eradiation/Cure (3)
600 mg	1 mef/Finland, 1 erm/US	0.06-0.12	Persistence/Fail (2)
<b>ABECB</b>			
300 mg	2 mef US and Germany	0.03-0.12	Eradiation/Cure (4)
600 mg	2 erm Italy and US 3 mef Germany & US, 1 erm Spain, 1 23S US	0.03-0.5	Eradiation/Cure (5)
<b>TOTAL</b>	18	0.03-4.0	16 Eradication/Cure (89%)



# PART 3

# Phase II Clinicals

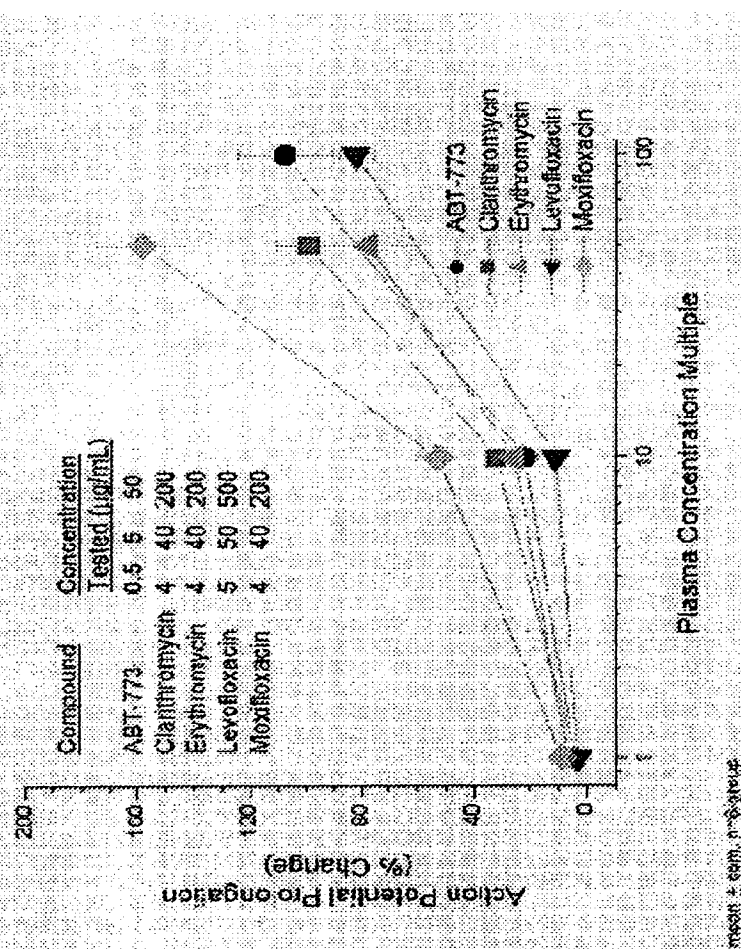
## Penicillin-Resistant *S. pneumoniae* Outcomes

	# of Isolates	Pen MIC	Bacteriologic/Clinical	Other Resistance
<b>CAP</b>				
300 mg	1/US	2	Eradication/Cure	Mef
600 mg	1/US	4	Eradication/Cure	Mef
<b>SINUSITIS</b>				
150 mg	1/US	2	Eradication/Cure	Susceptible
300 mg	1/Greece, 1/US	2	Eradication/Cure (2)	1 erm/Gre, 1 mef/US
600 mg	1/Finland, 1/US	2	Persistence/Fail (2)	1 erm/US, 1 mef/Fin
<b>ABECB</b>				
300 mg	3/US	2, 4	Eradication/Cure	mef
			Persistence/Fail	susc
			Persistence/Fail	susc
600 mg	1	4	Eradication/Cure	mef
<b>TOTAL</b>	11		8 Eradication/Cure	

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ABBT229405

# Comparative Effects of ABT-773 on Purkinje Fiber Pacemaker



## Phase II Clinicals

Subjects with  $\geq 3x$  increase in ALT/SGPT

	150 mg (n=223)	300 mg (n=322)	600 mg (n=318)
Within 48 hours after posttreatment	0.44% (1)	0.93% (3)	0.94% (3)
7-14 Days Posttreatment	0	0.62% (2)	0.31% (1)

## Phase II Clinicals

### Summary

- \* ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- \* ABT-773 was efficacious against all target pathogens
- \* All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- \* 150 mg QD will be evaluated in comparative studies of ABECB and pharyngitis in phase III
- \* 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

## Phase III Clinicals

### Proposed Indications and Treatment Duration

Pharyngitis/Tonsillitis	150 mg QD	5 days
Acute Bacterial Exacerbation of Chronic Bronchitis	150 mg QD	5 days
Community Acquired Pneumonia	150 mg QD or 150 mg BID	10 days
Acute Bacterial Sinusitis	150 mg QD or 150 mg BID	10 days

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# Phase III Clinicals

## Studies Started in Year 2000

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V 500 mg TID	260	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V 500 mg TID	260	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin 500 mg x1 250 mg QD	300	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin 500 mg QD	250	EU (Non-IND)

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ABBT229410

# Phase III Clinicals

Studies Started in Year 2000, con't

## Dose Finding Studies for Sinusitis/CAP:

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	600	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	800	US, Canada, EU (IND)



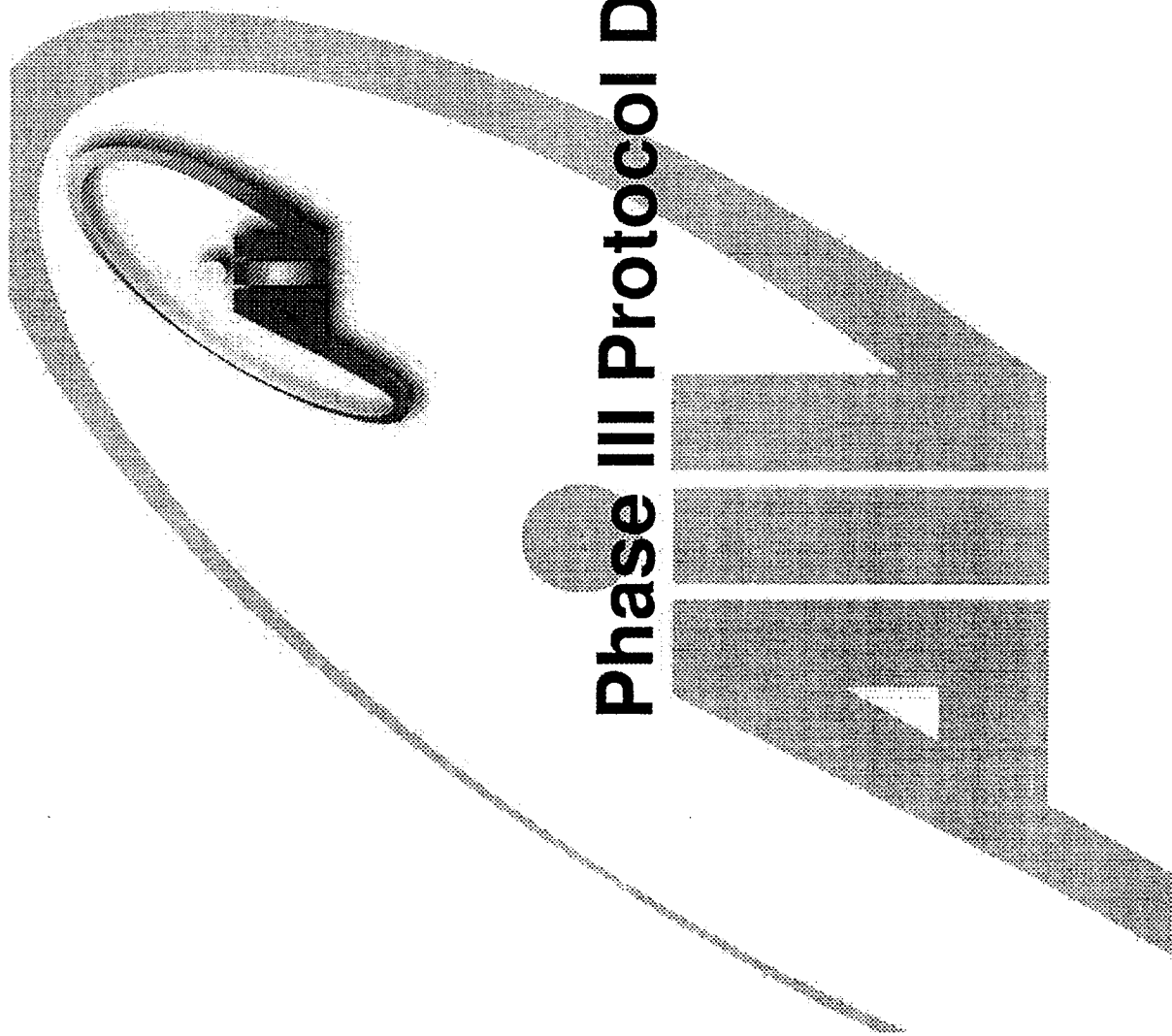
## Phase III Clinicals

Studies Starting in Year 2001

Study	Indication	Comparator	Number ABT-773 Subjects	Location
M00-221	CAP	Levofloxacin 500 mg QD	750	US, Canada (IND)
M00-220	CAP	Amoxicillin 1 gram TID	750	EU (Non-IND)
M00-226	Sinusitis	Augmentin 500 mg TID	660	US, Canada (IND)
M00-218	Sinusitis	Levofloxacin 500 mg QD	660	EU (Non-IND)

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# Phase III Protocol Design



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# Acute Bacterial Exacerbation of Chronic Bronchitis

Double-blinded, randomized, multi-center

N=500

ABT-773 150 mg QD X 5 days vs. Levofloxacin 500 mg QD X 7 days

Clinical Assessment: 7-14 days post treatment

## Major Inclusion Criteria

- 40 years of age or older
- History of chronic bronchitis: Cough and sputum production  $\geq 3$  consecutive months per year for  $> 2$  successive years
- Presumptive clinical diagnosis of acute bacterial exacerbation supported by at least 2 of the following (Anthonisen Criteria I and II):  $\uparrow$  dyspnea,  $\uparrow$  sputum volume,  $\uparrow$  sputum purulence
- Onset of ABECB exacerbation within 14 days of enrollment
- Qualifying purulent sputum ( $< 10$  epithelial and  $> 25$  leukocytes)

# Acute Bacterial Exacerbation of Chronic Bronchitis

## *Major Exclusion Criteria*

- Evidence of pneumonia or requires parenteral therapy
- Antibiotic therapy within two weeks of enrollment
- Serum creatinine 2.0 mg/dL or greater
- ALT, AST, Alk Phos or Total Bilirubin >2X ULN
- Immunosuppression
- Oral or parenteral steroids equivalent to daily dose of >10 mg prednisone



# Acute Bacterial Exacerbation of Chronic Bronchitis

## *Clinical Evaluations*

- Screening: Safety Labs, ECG, FEV1/FVC, sputum culture
- Study Day 3: ECG, Electrolytes and ABT-773 level
- Within 48 hours after completing treatment: ECG and Safety Labs
- 7-14 days after completing treatment: Safety Labs, FEV1/FVC, sputum culture
- 30 days after completing treatment: Clinical assessment





# Acute Bacterial Sinusitis

- \* Double-blinded, randomized, multi-center
- \* N=660
- \* ABT-773 150 mg QD or BID X 10 days vs. Levofloxacin 500 mg QD X 10 days
- \* Clinical Assessment: 7-14 days post treatment

## ***Major Inclusion Criteria***

- 18 years of age or older
- Clinical diagnosis of AMS lasting 7-28 days defined as one of following:
  - Facial pain, facial swelling, purulent discharge, toothache
- Sinus X-ray or CT consistent with sinusitis: opacification or air-fluid level
- Pre-treatment needle aspiration of sinus in subset of patients

# Acute Bacterial Sinusitis

## Major Exclusion Criteria

- Chronic sinusitis
- Antibiotic therapy within two weeks of enrollment
- Serum creatinine 2.0 mg/dL or greater
- ALT, AST, Alk Phos or Total Bilirubin >2X ULN
- Immunosuppression
- Requires parenteral therapy

# Acute Bacterial Sinusitis

## *Clinical Evaluations*

- \* Screening: Safety Labs, C-reactive protein, ECG, sinus puncture & culture
- \* Study Day 3-5: ECG, Electrolytes and ABT-773 level
- \* Within 48 hours after completing treatment: ECG and Safety Labs
- \* 7-14 days after completing treatment: Safety Labs, C-reactive protein
- \* 30 days after completing treatment: Clinical assessment



# Community-Acquired Pneumonia

- Double-blinded, randomized, multi-center
- N=750
- ABT-773 150 mg QD or BID X 10 days vs. Amoxicillin 1 Gram TID X 10 days
- Clinical Assessment: 7-14 days post treatment

## ***Major Inclusion Criteria***

- 18 years of age or older
- Clinical diagnosis based on at least two:
  - cough, fever, sputum production, dyspnea or tachypnea, auscultatory findings, WBC > 10,000/mm<sup>3</sup> or > 15% bands
- Qualifying purulent sputum (<10 epithelial and >25 leukocytes)
- Chest X-ray consistent with pneumonia

# Community-Acquired Pneumonia

## *Major Exclusion Criteria*

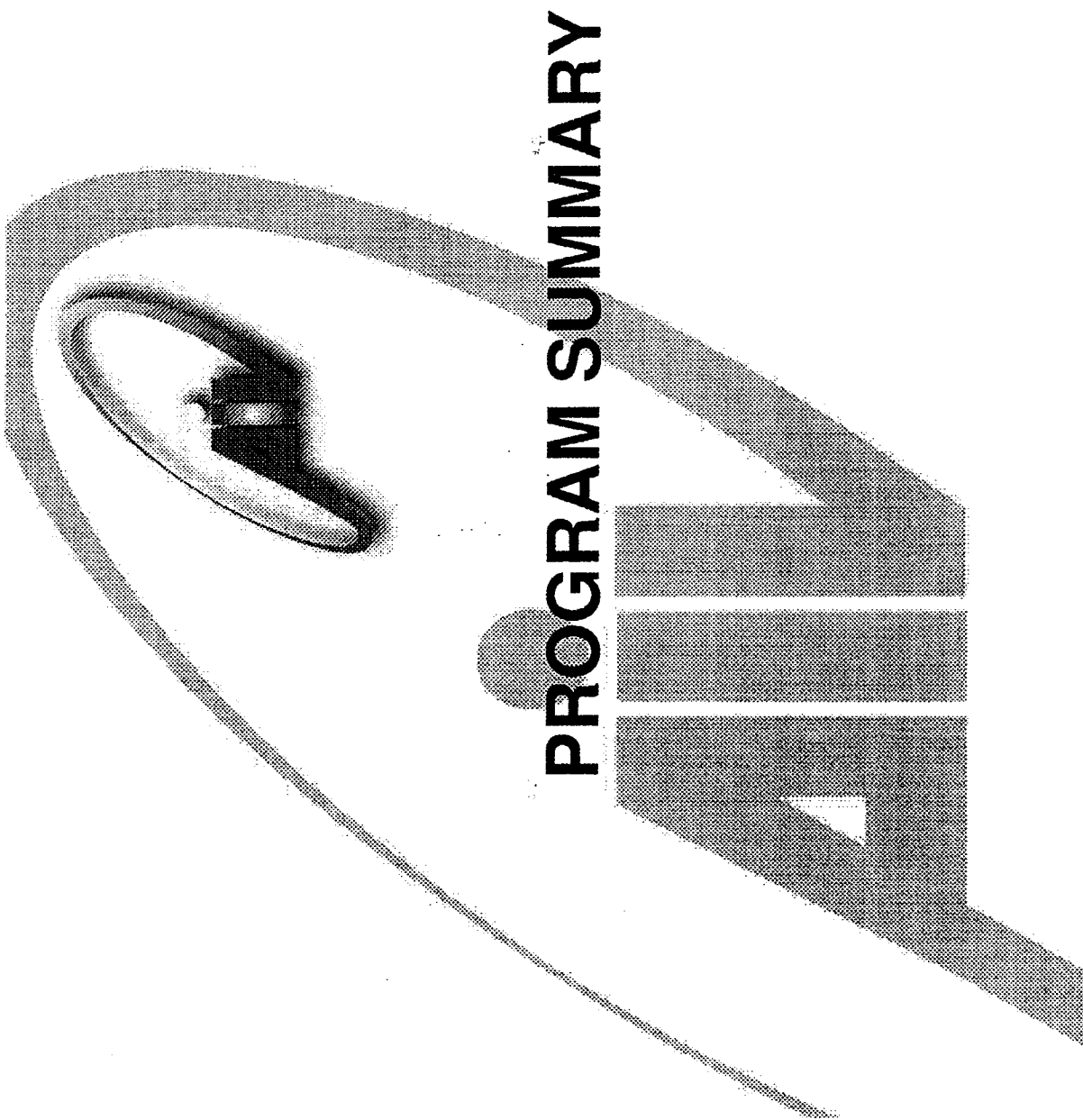
- \* Antibiotic therapy within two weeks of enrollment
- \* Serum creatinine 2.0 mg/dL or greater
- \* ALT, AST, Alk Phos or Total Bilirubin >2X ULN
- \* Immunosuppression
- \* Requires parenteral therapy
- \* 50 years of age or older + one of the following:
  - > respiratory rate >30/min
  - > SBP < 90 mm Hg
  - > T > 40 deg C or < 35 deg C
  - > pulse > 125/min

# Community-Acquired Pneumonia

## *Clinical Evaluations*

- \* **Screening:** Safety Labs, C-reactive protein, ECG, blood & sputum culture, atypical pathogen culture/ PCR/serology, urine Legionella Ag, Fine criteria
- \* **Study Day 4:** ECG, electrolytes and ABT-773 level
- \* **Within 48 hours after completing treatment:** ECG and Safety Labs
- \* **7-14 days after completing treatment:** Safety Labs, C-reactive protein, ECG, sputum culture, atypical pathogen culture & serology
- \* **30 days after completing treatment:** Clinical assessment

ABBT229423



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# ABT-773 Registration Package

	No. of ABT-773 Subjects	No. of Comparator Subjects
Community Acquired Pneumonia	1250	500
Acute Exacerbation of Chronic Bronchitis	676	550
Acute Bacterial Sinusitis	997	660
Pharyngitis	520	520
<b>TOTAL</b>	<b>3443</b>	<b>2230</b>

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ABBT229424



## SAE Summary Phase 2b

• M99-048 (6/384)	2%
• M99-053 (3/292)	1%
• M99-054 (14/187)	7.5%
• Total (23/863)	3%*

\*2 Expedited Reports

# SAE Summary

## • M00-216 ABECB

### – 14 SAEs

- 20041 Cardiomyopathy
- 20149 Pneumonitis and Labyrinthitis
- 20298 Unstable Angina
- 20273 Bilateral Pneumonia
- 20462 Worsening COPD
- 20326 Exacerbation of CB
- 20243 Chest Pain
- 20312 Pneumonia
- 20358 Pneumonia

- 20654 Chronic Bronchitis\*
- 20570 Chest Pain
- 20511 COPD
- 20508 COPD
- 20363 Vomiting\*

# PART 4



# SAE Summary

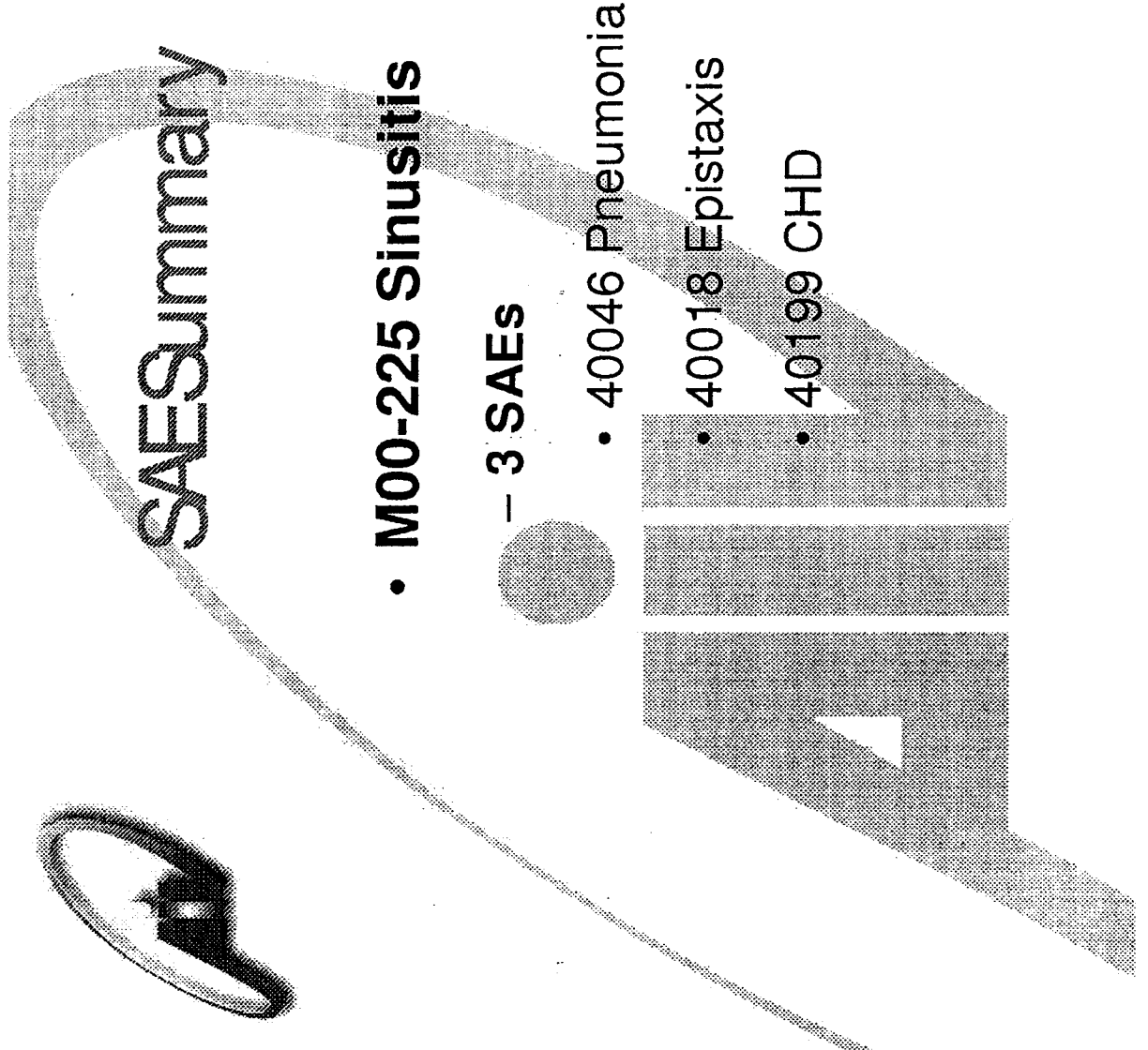
- **M00-219 CAP**
  - **18 SAEs**
    - 30043 Exacerbation of Asthma\*
    - 30341 Worsening Pneumonia\*
    - 30094 Electrolytes Imbalance
    - 30225 Phlebitis/Thrombus
    - 30462 Worsening Pneumonia\*
    - 30797 Sepsis\*
    - 30846 Worsening Pneumonia\*
    - 30227 Diarrhea and vomiting
    - 31013 Worsening Pneumonia\*
    - 31008 Worsening Pneumonia\*
    - 30049 UTI
    - 30846 Deep Venous thrombosis
    - 30349 Worsening Pneumonia\*
    - 30829 Depression
    - 30409 Worsening Pneumonia
    - 30409 Epsitaxis
    - 30409 Worsening Pneumonia
    - 30837 Asthma\*

# SAE Summary

- **M00-223 Pharyngitis**

- 5 SAEs

- 11296 Generalized Itching\*
    - 11447 Mononucleosis\*
    - 11398 Erythema Nodosum\*
    - 11325 Elective Abortion
    - 11598 Cholelithiasis\*



# SAESummary

- M00-225 Sinusitis

- 3 SAEs

- 40046 Pneumonia

- 40018 Epistaxis

- 40199 CHD

# SAE Summary

## Phase 3

• M00-216 (14/435)	2.2%
• M00-219 (18/298)	6.0%
• M00-223 (5/512)	1.0%
• M00-225 (3/425)	0.7%
• Total (40/1670)	2.4%

\* As of June 11, 2001

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# Pregnancies

- M00-223

- 3 SUBJECTS\*

- M00-225

- 1 SUBJECT

- Total 4 pregnancies



## S. pneumoniae Isolates

- CAP- 38: 11\* macrolide resistant (R) (29%): 3 ermB, 8 mefA
  - 5 penR (13%) 4 are also macrolide R, 1 is macrolide susceptible (s).
  - 773 MIC  $\leq$  0.25 mcg/ml for all isolates
  - 1 blood isolate clr/pen S
- Sinusitis- 28: 9 macrolide R (32%): 8 mef, 1 mef+erm
  - 4 penR (14%) 3 are macrolide R, 1 is macrolide S.
  - 773 MIC  $\leq$  0.12 mcg/ml for all isolates
- ABECB- 38: 9 macrolide R (24%): 4 ermB, 5 mefA
  - 2 penR (5%), both are macrolide R
  - (773 MIC  $\leq$  0.25 mcg/ml)
- Total- 104: 28% macrolide R;
  - 11% penR. Penicillin resistant isolates are likely (70-80%) to also be macrolide resistant. This is observed in our studies (82%).
  - No S. pneumo considered ABT-773 resistant by tentative breakpoints (0.5, 1, 2).

06/11/01

\* 8 confirmed in house

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## CAP update- subjects with resistant *S. pneumoniae*

- 248 subjects enrolled/ 134 subjects (54%) have culture with a target pathogen  $\geq 2+$ .
- 36 subjects have *S. pneumoniae* at pretreatment: 28% (36/134) of subjects with positive cultures and 15% (36/248) of all subjects.
- 11 subjects have *S. pneumo* isolates that are macrolide resistant, 4% of total subjects enrolled.
- 5 subjects have isolates that are penicillin resistant, 2% of total subjects. (4 of the 5 penicillin resistant strains are also macrolide resistant and are included in the 11 macrolide resistant strains). 80% of penicillin resistant isolates are also macrolide resistant.

06/11/01

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## H. influenzae

- CAP- 21 H flu (2-4+ )
  - 773 MIC range 0.015-4. No isolates MIC > 4.
- Sinusitis 40 H flu
  - 773 MIC range 1-8. 4 isolates MIC > 4.
- AECB 76 H flu (2-4+ )
  - 773 MIC range 0.06-8. 5 isolates MIC > 4.
- Overall 138 H flu 9 isolates MIC = 8
  - 6.5% intermediate, 0% resistant if using tentative breakpoints of 4, 8, 16.
  - MIC data are consistent with pre-clinical studies.

06/11/01

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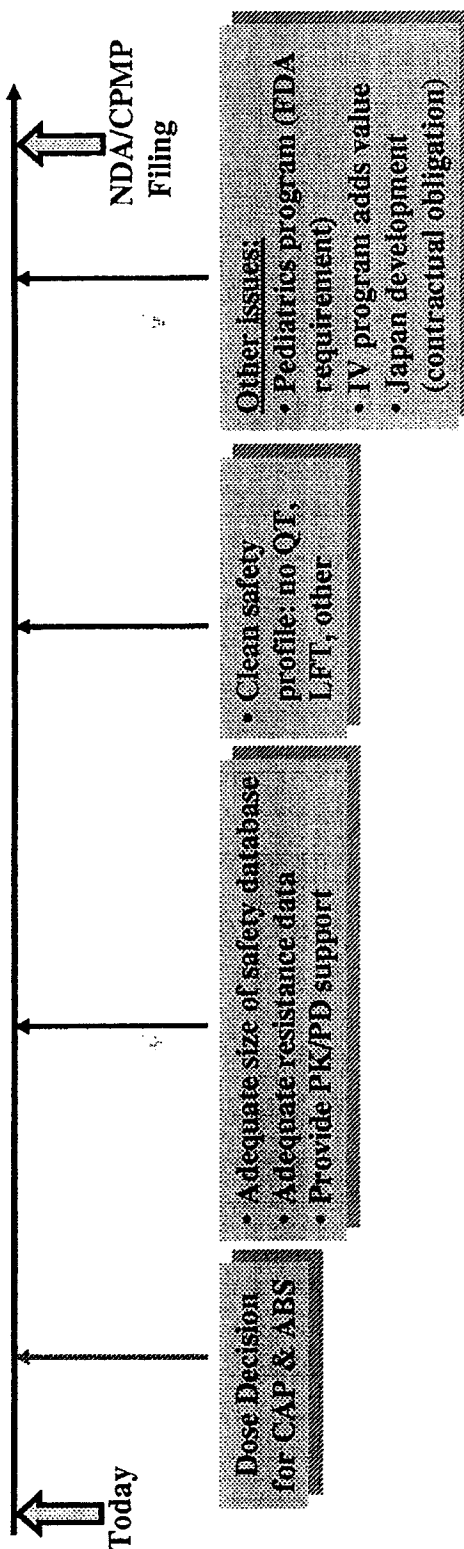
## S. pyogenes

- Acute streptococcal pharyngitis trial vs. penicillin
- 85% with positive eval 1 culture
- 21/420 isolates clari R (5%)
- 5 isolates with ABT-773 MIC  $\geq 1$  (1%)
  - 3 MIC=1, 2 MIC=2.
- 65/448 (15%) subjects with positive cultures at eval 4.

06/11/01

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*Filing date dependant on timing of Dose decision and Program size.  
Program size dependant on technical and regulatory hurdles*



3/2/2006

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ABBT229436

## *The Ketek advisory raised the hurdle for the approval of ketolides:*

- Size of the safety database is driven by the product benefit/risk profile.
  - Ketek's 3700 patient safety database insufficient.
  - ABT 773 benefit/risk is different for QD or BID dosing.
- A US resistance claim will significantly support benefit/risk
  - based on clinical cure rate of resistant isolates, with an emphasis on bacteremic patients (CAP indication only). Usual ratio 3:1
    - Ketek submitted 17 PRSP and MRSP isolates with 85% clinical cure and 6 bacteremics with 64% clinical cure. Levofloxacin was successful in obtaining resistance claim with 15 isolates and 6 bacteremics: 100% cure. ABT773 cure in Phase 2 was 73% sputa isolates, no bacteremia.
    - The Ketek advisory committee voted against a resistance claim; it is unknown if they will get a resistance claim

Isolates Needed	% CAP patients with PRSP/MRSP	
	1.4%	1.6%
17	1236	1063
25	1818	1563
30	2182	1875

**Current Phase 3 resistant isolate rate: 2% PRSP, supports CAP 1500 patients.**

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### *Safety database size issues.*

- Add to program: 500 CAP patients in pursuit of resistance claim  
300 ABS patients (double-tap 150; Ph3 150)

Outcome*	Safety Database		No. CAP Pts		Estimated no. isolates (50 <sup>th</sup> percentile)	
	Before	After	Before	After	Before	After
QD	4200	5000	1000	1500	17	25
BID	2400BID	3050 BID	750	1250	13	21
	1800QD	1950 QD				

Above assumes same dose ABS and CAP.

- Safety database needs more patients if BID dosing, increase less needed if QD dosing.
- Could add to safety with ABS patients (less time critical), but CAP patients allow for pursuit of resistance claim.
- To optimize chance of resistance claim, need IV program (Pediatric program could not catch up in time)

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*Phase IIIa current blinded data – ongoing studies.*

Indication (CRFs)	Clinical Response in Ph III Studies		
	Cure	Failure	Indeterminate
ABS (212)	155 (79%)	42	15
CAP (164)	125 (90%)	14	25
ABECB (330)	253 (86%)	55	22
ASP (360)	294 (86%)	46	20

• **Bacteriological response Ph3:**

- 54% pos isolates in CAP.
- 28% *S. Pnuemo*
- 4% MRSP, 2% PRSP
- 1 bacteremia

**Bacteriological cure rate Phase II studies.**

863 patients sputa cultures  
11 PRSP.  
Cured 73% (8/11).

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*Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.*

Strategic Alternative	Description
Use ABS & CAP dose-ranging data	<ul style="list-style-type: none"> <li>• Complete current ABS &amp; CAP dose-ranging trials and then make dose decision.</li> <li>• Complete Phase III pivotal with selected dose.</li> </ul>
Use ABS dose-ranging data only	<ul style="list-style-type: none"> <li>• Complete only the ABS dose-ranging study and then make a dose decision for both ABS &amp; CAP.</li> <li>• If QD succeeds in ABS, obtain regulatory approval for conducting QD CAP pivotal.</li> </ul>
Select BID today	<ul style="list-style-type: none"> <li>• Select the BID dose today for ABS &amp; CAP Ph III pivotal.</li> <li>• Do not wait for completion of the dose-ranging studies.</li> </ul>
Select QD Today	<ul style="list-style-type: none"> <li>• Select the QD dose today for ABS &amp; CAP Ph III pivotal.</li> <li>• Do not wait for completion of the dose-ranging studies.</li> <li>• US &amp; EU regulatory non-viability.</li> </ul>
QD in the US & BID in the EU	<ul style="list-style-type: none"> <li>• Develop BID in CAP &amp; ABS for EU; Develop QD for US.</li> <li>• Clinical program requires 3 simultaneous CAP comparator studies -- unacceptable costs and timelines.</li> </ul>
Phase III 3-arm CAP & ABS pivotal	<ul style="list-style-type: none"> <li>• Expand the Phase III CAP program to allow for 3 arms per study -- QD vs. BID vs. comparator.</li> <li>• Very high technical/statistical risk and defers dose decision.</li> </ul>

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### *Immediate path ahead*

- Prepare ABS and CAP trials for both doses so no time delay on decision.
- Ensure critical timeline of ABS dose decision-database lock dependant on CRF finalization.
- Continue to refine criteria for dose decision
- Ensure early meeting with Agencies to a priori investigate extrapolation of QD dose from ABS to CAP under pretext of QT trial.
- Ensure timelines of IV program on track assuming funding.
- Rollover ABS (and CAP) into open label trials to ensure ongoing site participation.

3/2/2006

6

*Anti-infective Venture / GNFP / Decision Support Group*

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## Ketek Clinical Trial Summary

AEGB #1	Ketek 800 mg QD x 5d	Cefitin 500 mg BID x 10 d
Cure	88%	86%
Eradication	88%	86%
-S.pneumo	100%	75%
-H. flu	88%	85%
Diarrhea	11%	10%
Nausea	9%	3%
Dizziness	NS	NS
AEGB #2	Ketek 800 mg QD x 5d	Augmentin 500 mg TID x 10 d
Cure	86%	82%
Eradication	69%	70%
AEs (combined)	24%	37%
AEGB #3	Ketek 800 mg QD x 5d	Biaxin 250 mg x 10 d
Cure	91%	91%
Eradication	91%	89%
Diarrhea	17%	8%
Nausea	11%	4%
Dizziness	6%	1%
AEGB #4	Ketek 800 mg QD x 5d	Pen V 500 mg TID x 10 d
Cure	84%	94%
Eradication	12%	89%
Diarrhea	6%	3%
Nausea	3%	1%
Dizziness	3%	1%

CAP #1	Ketek 800 mg QD x 10d	Biaxin 500 mg BID x 10 d
Cure	89%	89%
Eradication	89%	96%
-S.pneumo	94%	93%
-H. flu	78%	100%
Diarrhea	13%	7%
Nausea	9%	5%
Dizziness	4%	2%
CAP #2	Ketek 800 mg QD x 7-10d	Trovan 200 mg QD x 7-10d
Cure	91%	95%
Eradication	94%	100%
Diarrhea	17% (sig.)	6%
Nausea	8%	4%
Dizziness	2%	7%
CAP #3	Ketek 800 mg QD x 7-10d	Amoxicillin 1 g TID x 10 d
Cure	95%	90%
Eradication	88%	87%
-S.pneumo	96%	86%
-H. flu	75%	85%
Diarrhea	10%	8%
Nausea	8%	4%
Dizziness	NS	NS
CAP #4	Ketek 800 mg QD x 7-10d	None
Cure	85%	-
Eradication	89%	-
Diarrhea	8%	-
Nausea	5%	-
Dizziness	NS	-
AEGB #1	Ketek 800 mg QD x 10d	Augmentin 500 mg TID x 10d
Cure	74%	75%
Eradication	86%	75%
Diarrhea	20%	24%
Nausea	NS	NS
Dizziness	NS	NS
AEGB #2	Ketek 800 mg QD x 5d	Ketek 800 mg QD x 10 d
Cure	91%	91%
Eradication	91%	91%
-S.pneumo	93%	89%
-H. flu	100%	85%
Diarrhea	10%	13%
Nausea	5%	2%
Dizziness	NS	NS
AEGB #3	Ketek 800 mg QD x 5d	Augmentin 500 mg TID x 10 d
Cure	74%	75%
Eradication	86%	75%
Diarrhea	19%	24%
Nausea	12%	8%
Dizziness	5%	2%

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7

Anti-infective Venture / GNPP / Decision Support Group



*The QD/BID dose decision depends on a number of technical trade-offs.*

Issue	150 mg QD	150 mg BID
Efficacy	<ul style="list-style-type: none"> <li>• Blinded data suggest good efficacy.</li> <li>• French authorities expressed skepticism for QD dose in CAP.</li> </ul>	<ul style="list-style-type: none"> <li>• Higher probability of success in all indications, including resistance.</li> </ul>
Safety Database	<ul style="list-style-type: none"> <li>• Larger database (can use both QD and BID data).</li> </ul>	<ul style="list-style-type: none"> <li>• May need larger number of patients in a two-dose program.</li> </ul>
Tolerability	<ul style="list-style-type: none"> <li>• Higher probability of favorable profile.</li> </ul>	<ul style="list-style-type: none"> <li>• Potential for less favorable profile.</li> </ul>
QT effects	<ul style="list-style-type: none"> <li>• Lower risk of QT effect.</li> </ul>	<ul style="list-style-type: none"> <li>• Lower safety margin for QT effect given potential CYP3A interactions.</li> </ul>
PK/PD	<ul style="list-style-type: none"> <li>• Higher hurdle for dose justification.</li> </ul>	<ul style="list-style-type: none"> <li>• More favorable PK/PD assessment.</li> <li>• Must study diurnal variation effect.</li> </ul>
CAP data support of ABECB	<ul style="list-style-type: none"> <li>• Favorable CAP results can be used to support ABECB indication.</li> </ul>	<ul style="list-style-type: none"> <li>• Different dosing in CAP and ABECB prevents use of CAP results to support ABECB.</li> </ul>

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ABBT2294433

*The requirements for the ABT-773 clinical development program have changed since the dose-ranging study began.*

At Phase III initiation (09/00)	Since then...	Impacts on program
Planned a QD/BID dose-ranging study to find optimum dose for CAP & ABS.	Administrative delays at the FDA and slow recruitment (poor flu season) delay the study.	Unable to complete dose-ranging in time to allow for initiation of pivotal in Sep/01 (northern hemisphere flu season).
Safety database designed to contain 2700-3200 patients.	Ketek submitted 3700 patients, which was deemed insufficient by the advisory.	Program size increased to include ~4500 patients.
CAP pivotal designed only to achieve CAP indication – not a resistance claim.	Ketek advisory revealed the importance of the resistance claim, especially if there are safety concerns.	Regulatory approval will depend, in part, on ABT-773's ability to achieve a resistance claim.
CAP not considered a requirement for regulatory approval.	Ketek advisory heavily focused on benefit/risk, especially for CAP.	US Regulatory Affairs increases the importance of the CAP indication for drug approval.
Requirements for the resistance claim assumed to be similar to Levaquin.	Ketek submitted 17 isolates with 86% cure rate – deemed insufficient by advisory.	The size of the program has been increased to allow a 50% probability of enrolling 25 resistant isolates (double the number of CAP patients).

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9 Anti-infective Venture / GNPP / Decision Support Group

## *S. pneumoniae* Isolates

- CAP- 38: 11\* macrolide resistant (R) (29%): 3 ermB, 8 mefA
  - 5 penR (13%) 4 are also macrolide R, 1 is macrolide susceptible (S).
  - 773 MIC <0.25 mcg/ml for all isolates
  - 1 blood isolate clr/pen S
- Sinusitis- 28: 9 macrolide R (32%): 8 mef, 1 mef+erm
  - 4 penR (14%) 3 are macrolide R, 1 is macrolide S.
  - 773 MIC <0.12 mcg/ml for all isolates
- ABECB- 38: 9 macrolide R (24%): 4 ermB, 5 mefA
  - 2 penR (5%), both are macrolide R
  - (773 MIC <0.25 mcg/ml)
- Total- 104: 28% macrolide R;
  - 11% penR. Penicillin resistant isolates are likely (70-80%) to also be macrolide resistant. This is observed in our studies (82%).
  - No *S. pneumo* considered ABT-773 resistant by tentative breakpoints (0.5, 1, 2).

\*8 confirmed in house



*CAP update- subjects with resistant S. pneumoniae Ph 3 dosing*

	Numbers (%)	MIC
Subjects enrolled	248	
Subjects with positive cultures pre rx	134 (54%)	
Subjects with S.Pneumo preRx	38 (28%, 15%)	
MRSP	11 (4%)	3 ermB, 8 mefA 773MIC <0.25mcg/ml for all isolates
PRSP	5 (2%)	
MRSP and PRSP	4 (80%)	

11 Anti-infective Venture / GNPP / Decision Support Group

3/2/2006

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*H. influenzae*

CAP	- 21 H flu	773 MIC range 0.015-4.	No isolates MIC>4.
Sinusitis	40 H flu	773 MIC range 1-8.	4 isolates MIC>4.
AECB	76 H flu	773 MIC range 0.06-8.	5 isolates MIC>4.
Overall 138 H flu 9 isolates MIC=8	6.5% intermedi- ate,,	0% resistant if using tentative breakpoint of 4, 8,	

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12 Anti-infective Venture / GNPH / Decision Support Group

ABBT229447

## *S. pyogenes*

- Acute streptococcal pharyngitis trial vs.. penicillin
- 85% with positive eval 1 culture
- 21/420 isolates clari R (5%)
- 5 isolates with ABT-773 MIC >1 (1%)
  - 3 MIC=1, 2 MIC=2.
- 65/448 (15%) subjects with positive cultures at eval 4.

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13 Anti-infective Venture / GNPP / Decision Support Group

ABBT229448

**654**

## ABT-773 Ketolide Antibiotic - Tablet

Franchise	Dev. Status	Brand Name	Generic Name	Patent Exp.	2017	Indication(s)																																																																														
Anti-Infective	Phase III	Under Development	Pending			Bronchitis, pharyngitis/sinusitis, community-acquired pneumonia, sinusitis																																																																														
<ul style="list-style-type: none"> <li>ABT-773 is a potent antibiotic that has excellent activity against respiratory pathogens, including penicillin/macrolide resistant <i>S. pneumoniae</i></li> <li>ABT-773 will be dosed 150 mg QD x 5 days for AECB and pharyngitis, dosing for CAP and sinusitis will likely be 150 mg BID x 10 days</li> <li>ABT-773 will compete with macrolides on the basis of superior activity against resistant organisms (resistance claim being pursued) and improved mechanism and against quinolones on the basis of appropriate use and safety</li> <li>BID dosing for CAP and sinusitis will present commercial challenges</li> </ul>																																																																																				
Description																																																																																				
U.S. Market	Unit	Value	%95-00	Unmet Need/Key Market Drivers																																																																																
	TRX	217 MM	0.1%	Unmet need in community RTI is relatively low. Key market drivers are resistance (ability to treat resistant organisms along with low propensity to develop resistance), tolerability, and convenience. A number of key antibiotics lose patent exclusivity in 2003-2005 (Biaxin, Zithromax, Levaquin, Cipro), which may negatively impact future prices																																																																																
	Sales	\$6,081 MM	9.5%																																																																																	
Ex-U.S. Market	TRX	524 MM	0.4%	Need exists for agents active against pen and macrolide resistant pathogens without the safety concerns currently associated with the quinolone class. Pharmacoeconomic issues are of increasing concern to government-controlled healthcare systems, leading to higher hurdles for regulatory approval regarding therapeutic benefit vs. existing therapies, strict price/reimbursement controls, and push for shorter courses of therapy																																																																																
	Sales	\$6,644 MM	5.9%																																																																																	
Development to NDA, excludes Japan)	Cost to NDA	Thru 2000	YTD	2001	2002	2003	2004	2005	2006	2007	2008	Post LRP	Total																																																																							
	Chiracals	NA	\$36.9	\$41.0	\$62.2	\$0.0	\$36.9	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$138.0																																																																							
	CMC	NA	\$77.3	\$48.6	\$20.5	\$0.0	\$14.5	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$112.3																																																																							
	Drug Safety	NA	\$8.8	\$1.2	\$1.9	\$0.0	\$1.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$11.7																																																																							
	Other	NA	\$31.3	\$2.5	\$3.9	\$0.0	\$5.9	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$41.1																																																																							
	TOTAL	\$200.0	\$153.3	\$53.3	\$88.5	\$0.0	\$51.3	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$303.1																																																																							
Commercial (excludes Japan)	<p><b>Base Case Forecast</b></p> <p><b>Financial Summary</b></p> <table border="1"> <thead> <tr> <th>Year</th> <th>2005</th> <th>2006</th> <th>2007</th> <th>2008</th> <th>2009</th> <th>2010</th> <th>2011</th> <th>2012</th> <th>2013</th> <th>2014</th> </tr> </thead> <tbody> <tr> <td>Peak Sales (\$MM)</td> <td></td> <td></td> <td>\$248</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Peak Standard Margin (\$MM)</td> <td></td> <td></td> <td>\$224</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Peak Standard Margin (%)</td> <td></td> <td></td> <td>90.5%</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Expected Value (Global, \$MM)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>160</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p><b>Commercial Profile</b></p> <p>Launch Date: Jan 05 Price per Day at Launch (AWP): \$8.78 Comparable to Z-Pak Sales force @ peak sales (\$MM): \$62 Promo @ peak sales (\$MM): \$47 COGS @ launch @ peak: \$3,000/kg, \$1,500/kg Market/External/Other: New launches in 2013, additional quinolone entrant, market TRX (at)</p> <p><b>Product Profile (Efficacy, Safety, Convenience)</b></p> <p>Efficacy: Comparable cure/eradication rates (75-90%) vs comparators Safety/AE: Resistance claim being targeted at launch Safety/AE: Adverse events comparable to Biaxin XL Safety/AE: No major safety issues/product-specific labelling Conven: 150 mg QD x 5 days dosing for AECB &amp; pharyngitis Conven: 150 mg BID x 10 days dosing for CAP &amp; sinusitis at launch Conven: QD line extension in CAP &amp; sinusitis in year 2 post-launch</p> <p><b>Base Case Assumptions (to be revised in light of ongoing DSG analysis)</b></p> <p>Taste: 5% Nausea: 5% Diarrhea: 5-10%</p> <p><b>Prob State Impact</b></p> <table border="1"> <thead> <tr> <th>Prob</th> <th>State Impact</th> </tr> </thead> <tbody> <tr> <td>Medium</td> <td>High</td> </tr> <tr> <td>Medium</td> <td>Medium</td> </tr> <tr> <td>Medium</td> <td>High</td> </tr> <tr> <td>Medium</td> <td>High</td> </tr> <tr> <td>Medium</td> <td>High</td> </tr> <tr> <td>Medium</td> <td>High</td> </tr> <tr> <td>Medium</td> <td>High</td> </tr> </tbody> </table> <p><b>Ex-U.S.</b></p> <p>Mar-05: Equivalent to current claz 750 mg BID pricing Mar-05: \$2.22 Mar-05: \$56 Mar-05: \$27 Mar-05: \$3,000/kg, \$1,500/kg Mar-05: Quinolones used primarily in more severe RTI segment Mar-05: Ketak on market 4Q01 with inferior tolerability profile vs ABT-773</p>													Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Peak Sales (\$MM)			\$248								Peak Standard Margin (\$MM)			\$224								Peak Standard Margin (%)			90.5%								Expected Value (Global, \$MM)						160					Prob	State Impact	Medium	High	Medium	Medium	Medium	High	Medium	High	Medium	High	Medium	High	Medium	High
Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014																																																																										
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Next Go/No Go Business Rationale	<p>Receipt of Phase III data 3-4Q01, dose selection for CAP &amp; sinusitis</p> <p>ABT-773 represents a key product for the global anti-infective franchise given the patent expiration of clarithromycin 2004-2005. The product has a compelling selling proposition by virtue of its novel ketolide class and its activity against resistant organisms, provided it can deliver on safety, tolerability, and convenience dimensions. Ketak regulatory issues in US may present opportunity. Likely BID dosing in some indications and relatively low PK profile represent potential issues.</p>																																																																																			

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**July 2001****ABT-773****Monthly Highlights – Key Project Progress**

- The Decision Analysis process was completed and presented to senior management on July 25<sup>th</sup>, recommending that the Phase III comparator studies for CAP and ABS be conducted with the 150mg BID dose. We have reached a target of 500 patients enrolled in the ABS QD vs BID however, and will have the unblinded results available by the end of Sept. to confirm the BID decision.
- The Phase III CAP and ABS study sizes have been increased to improve the chances of obtaining adequate resistant isolates to support our request for a claim for resistance in the label. Also, based on experience gained from the Ketek FDA advisory, we have increased the size of the safety database. Further confirmation of the adequacy of this database will be pursued with the FDA.
- Based on the above changes to the Phase III program, we are re-assessing timelines to the NDA and anticipate a delay beyond the current target of Aug 2002.
- The Phase I QT study protocol is currently being reviewed at FDA and we anticipate written comments from FDA by mid-August.
- The initial Phase I study for the IV formulation will be dosing October 8<sup>th</sup> to evaluate dose levels, concentration and rates of infusion. Based on positive results and a Go decision, we plan to do further Phase I evaluation by the end of 2001 and start Phase III in mid-2002. An IV formulation will provide further support for the tablet filing.
- An assessment of the Pediatric development to-date was completed, and a proposal to move forward with further formulation development and Phase I studies has been developed. FDA guidelines for a pediatric formulation require companies to show due diligence with a pediatric development program. A pediatric proposal will be made to senior management.
- The Japan development program is progressing with plans being made to initiate an open label study and a BAL tissue study at the end of 2001. At the completion of the open label study in 2002, a meeting with KIKO is planned to present the Phase III plan and address the potential of a bridging strategy.

**Next Quarter's Key Progress Markers:**

Key Progress Marker	Target Date
Complete classification and break the study blind for 500 ABS subjects in M00-225 study (150mg QD vs BID)	10/01
Complete final protocol and study preparation activities for the Phase III CAP and ABS pivotal studies (US and European) and initiate enrollment.	11/15
Conduct teleconference with FDA regarding Phase I QT study.	8/31
Initiate Phase I QT study.	11/01
Initiate first Phase I study of IV formulation.	10/08
Initiate Japan Open Label and BAL Tissue studies.	12/01
Initiate further formulation development on the pediatric prototypes.	09/28
Complete study classification and preliminary results for US Pharyngitis study M00-223, first Phase III comparator study to complete.	09/28
Complete European Pharyngitis (M00-222) and both European and US ABECB (M00-216 & M00-217) study enrollment.	12/31
Complete M01-311 definitive bioequivalence study (300L intermediate scale vs 1200L commercial scale)	11/30

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July 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
150 mg QD vs BID dose decision in CAP/sinusitis.	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing would result in a negative commercial impact.	Dose decision of 150mg BID was recommended to senior management on July 25 <sup>th</sup> . ABS QD vs BID results will be available by the end of Sept. to provide further confirmation of the decision, but at this time plans are going forward to initiate BID comparator studies for CAP and ABS in November.	Venture/NPD/DSG	7/2001/7/2001
Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product.	Acute tox study in conscious dog showed no difference from the earlier sedated dog study. The Phase I QT study protocol is under review at FDA and written comments are expected mid-August. An FDA conference regarding Ph 1 QT has been requested. Study initiation following FDA protocol acceptance.	Regulatory	6/2002
The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially; particularly with respect to <i>H. influenzae</i> .	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Support by PK/PD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model.	Internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts to define further study. BAL tissue studies with 150mg QD and BID are ongoing.	Venture/NPD	07/2002
Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim.	FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. The Keltek FDA experience indicates that number of isolates, clinical success, and patient severity all figure into their decision. Based on DSG analysis, we have increased our CAP studies to include 1500 patients to target 25 resistant isolates to support the resistance claim.	Venture	06/2002

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July 2001

ABT-773

## Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
Phase I was repeated in Japan to further evaluate dose-ranging. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	<input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	The Japan Phase I Dose-Ranging study results showed no difference between Japanese and Caucasians subjects and did not show liver elevations as seen in the Hawaii study. Based on our meeting in June in San Diego, Japan will proceed to plan a Phase II Open Label study and Phase I BAL Tissue study by the end of 2001.	Japan	08/2001/06/2001
The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed.	<input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding.	The single-rising dose Phase I study protocol has been amended to incorporate changes to doses, concentrations used and infusion times to allow for additional evaluation of QT effects within this study. The study is planned to start in October. A Go/No go decision on the IV formulation can be made once results are available (Dec. 2001).	HPD, Venture	09/2001
In light of the Ketec advisory focus on hepatic toxicity an a similar analysis of liver function tests has been undertaken for ABT 773	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	A benchmark comparison to Clarithromycin as well as Ketec data is being undertaken. Visit to Univ of Texas opinion leader undertaken. Current data in his opinion will not adversely affect approvability. Ongoing safety reviews of LFT data planned at appropriate intervals.	Venture	05/31

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**July 2001****ABT-773****Key Activities****Commercial**

Activity	LBE	Actual
Completion of study tracking intranet	3001	
Integration of intranet into communication plan	3001	
Integration of intranet into draft product label	3001	
Identification of communication vendor	3001	
Submission of brand/USAN names	2001	Ceftriaxone or velamycin pending approval by WHO; Affina & Actega to be submitted to FDA 7/01
Preliminary qualitative positioning research	1002	
Quantitative market research to support revised forecast	1002	
Preliminary qualitative positioning research	1002	

Activity	Formulation	Plan	Actual	Plan Date: 12/98
Phase I Formulation (Caps)*		12/1997	12/1997	
Phase II Formulation (Tablet)		7/1999	8/1999	
Clinical Supplies Phase IIB		7/1999	8/1999	
Phase III Formulation (Tablet)		4/2000	7/2000	
Phase III Clinical Supplies Manufactured		9/2000	9/2000	
NDA Lots (3) Completed		7/2000	01/2001	
Completion of 1 Year Stability for NDA		8/2001		
Formulation Peer Review		11/2001		

**Drug Substance****Plan Date:**

Activity	KG	Plan	Actual	Actual Projected Cost/kg
----------	----	------	--------	-----------------------------

See the following page for a  
summary of Bulk Drug  
deliveries in SPD.

Toxicology Activity	Plan Start 7/01/97	Actual Start Date	Report Completed	Plan Date: 12/98
2-week oral Rat/Monkey	7/1997	6/1997	9/1998	
Acute Studies	8/1997	8/1997	12/1997	
Mouse Lymphoma/Micronucleus	11/1997	11/1997	4/1998	
1 Month Rat/Monkey	12/1997	12/1997	12/1998	
Pregnant Rat/Rabbit RF	1/1998	1/1998	11/1998	
SEG II Rat/Rabbit	3/1998	3/1998	2/1999	
Guinea pig sensitization	11/1998	11/1998	2/1999	
3 Month oral Rat/Monkey	9/1999	10/8/1999	8/2000	
Seg III Rat	9/1999	10/8/1999	12/2001	
IV Irritation studies, set 1	7/1999	7/15/1999	8/1999	
IV Irritation studies, set 2	2/2000	2/2000	3/2000	
IV 2-week Rat/Monkey Studies	6/2000	6/2000	01/2001	
Neonatal/Juvenile Rat	10/1999	11/1999	7/2000	

\* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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SPD ABT-773 Bulk Drug Deliveries Update						
	Target Date	Amount	Delivery Date	Amount	Lot #	Amount after milling
Campaign 1	2/28/99	200 Kg	2/23/99	209 Kg	50-007-CA-00	207.5 Kg (2/26)*
Campaign 2a	6/15/99	140 Kg	6/17/99	131 Kg	54-702-NI-00	129.4 Kg (6/19)*
Campaign 2b	7/15/99	140 Kg	7/21/99	121.5 Kg	55-208-CB-00	119.3 Kg (8/4)*
Tox lot	8/30/99	5 Kg	8/25/99	6.1 Kg	55-718-NI-00	
Campaign 3a	9/30/99	160 Kg	10/8/99	170.5 Kg	58493CB00	138.4 Kg (10/16)*
Campaign 3b	10/21/99	160 Kg	10/11/99	176.5 Kg	58494CB00	169.5 Kg (10/16)*
Pilot run 1	*****	15 Kg	10/30/99	18.9 Kg	59763N100	no milling
Pilot run 2	*****	15 Kg	2/5/00	15.5 Kg	61790NI00	no milling
Pilot run 3	*****	25 Kg	1/30/00	27.5 Kg	62764CB00	27.3 Kg (4/18)*
Campaign 4	12/10/99	320 Kg	11/23/99	355 Kg	61741CB00	309 Kg (3/2)*
Campaign 5	12/30/99	300 kg	12/16/99	300.5 Kg	60665CB00	269.2 Kg (3/3)*
Campaign 6	2/28/00	280 Kg	2/23/00	321 Kg	62796CB00	315.5 Kg (3/6)*
Campaign 6 (IV)	2/28/00	15 Kg	2/22/00	20 Kg	62797CB00	18 Kg (3/15)*
Campaign 7	3/30/00	300 Kg	4/10/00	370 Kg	63890CB00	361.2 Kg (4/18)*
Campaign 7 (IV)	3/30/00	5 Kg	3/29/00	19 Kg	63889CB00	17.2 Kg (4/11)*
Campaign 8	4/25/00	200 Kg	5/11/00	263 Kg	64970CB00	256.5 Kg (5/15)
Campaign 8 (IV)	4/25/00	15 Kg	4/25/00	19.8 Kg	64971CB00	17.7 Kg (5/11)*
Campaign 9	6/15/00	300 Kg	6/14/00	375.7 Kg	65064CB00	355.7 Kg (6/20/00)
Campaign 9 (IV)	6/15/00	15 Kg	6/5/00	18.1 Kg	65065CB00	16.7 Kg (6/9/00)*
Campaign 10	7/15/00	300 Kg	7/26/00	361.2 Kg	67176CB00	359.0 Kg (8/10/00)
Campaign 11	8/15/00	300 Kg	8/4/00	333.7 Kg	68285CB00	271.9 Kg (9/7/00)
Campaign 12	10/6/00	300 Kg	9/27/00	356 Kg	69458CB00	292.3 Kg (12/8/00)
Campaign 13	11/23/00	300 Kg	11/15/00	351.2 Kg	71665CB00	349.1 Kg (12/20/00)
Total (year 2000)					2,815.5 Kg	
Campaign 14	1/28/01	300 Kg	1/26/01	327.5 Kg	73886CB00	318.9 Kg (02/13/01)
Campaign 15	2/10/01	330 Kg	1/14/01	354.9 Kg	71699CB00	353.8 Kg (02/02/01)
* Weight after rework						

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ABT-773

## All Clinical Studies:

Protocol Number	Phase	Study Name	Start 1 <sup>st</sup> Pl. Dosed	End (Last CRF In)	Patients		Protocol Number	Phase	Study Name	Start 1 <sup>st</sup> Pl. Dosed	End (Last CRF In)	Patients	
					Target	Current						Target	Current
M99-048	II	Dose Ranging, ABECB	9/1/99	3/31/00	300	384							
M99-053	II	Dose Ranging, Sinusitis	9/1/99	4/30/00	300	292							
M99-054	II	Dose Ranging CAP	9/1/99	4/30/00	300	187							
M00-219	III	CAP, Dose Ranging	11/7/00	12/31/01	800	358							
M00-216	III	ABECB vs Azithromycin	11/7/00	12/31/01	600	456							
M00-217	III	ABECB vs Levofloxacin	11/7/00	12/31/01	500	178							
M00-225	III	Sinusitis Dose Ranging	11/7/00	12/31/01	600	515							
M00-223	III	Pharyngitis vs Penicillin 500mg TID	11/7/00	8/30/01	520	522							
M00-222	III	Pharyngitis vs Penicillin 500mg TID	11/7/00	12/31/01	520	86							
M01-325	I	QT Phase I Study	09/01	12/30/01	68	0							
M01-331	I	IV Single Dose study	10/8/01	12/31/01	64	0							
M01-311	I	Definitive Bioassay	08/02/01	09/30/01	81	26							

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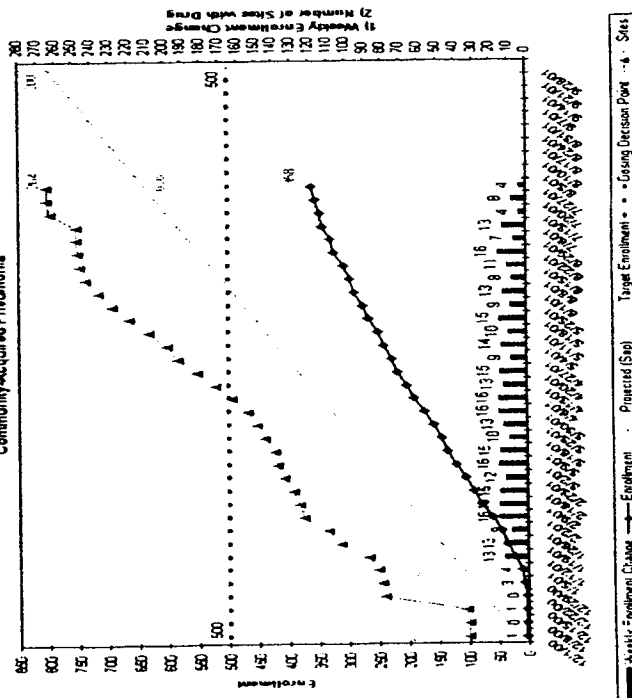
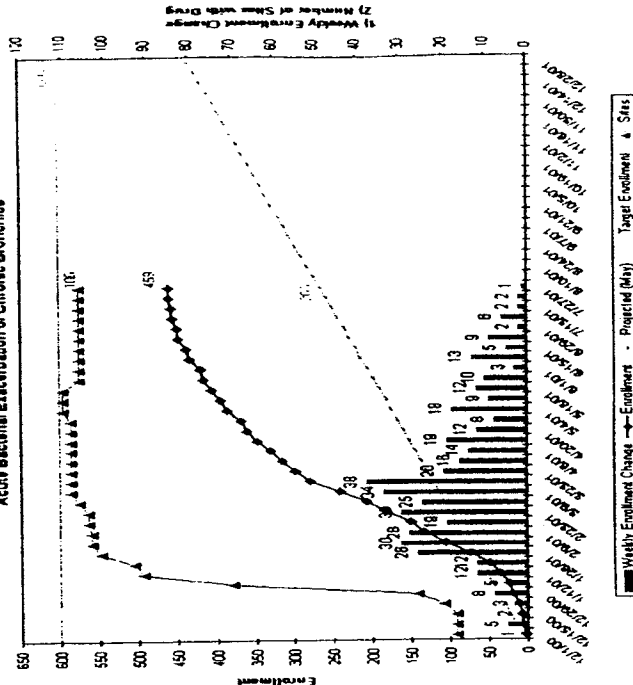


**July 2001****ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

**Protocol:** Dose selection.  
**Objective:** 150mg QD vs 150mg BID, 10 days  
**ABT-773 Doses:** None  
**Comparator Doses:** 800  
**Target Enrollment:** Currently enrolling  
**Status:** Currently enrolling  
**Major Findings:**

**M00-219 – Dose-Ranging CAP**

**M00-216 – Phase III ABECB vs Azithromycin**  
**Safety & Efficacy**  
 150mg QD, 5 days  
 Azithromycin 500mg day 1, 250mg QD for 4 days  
 600  
 Currently Enrolling

**M00-219 CAP Study (All Sites)**  
Community-Acquired Pneumonia**M00-216 ABECB Study (U.S. Sites)**  
Acute Bacterial Exacerbation of Chronic Bronchitis

8 of 10

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**ABBT 0000696****HIGHLY CONFIDENTIAL – FOR INTERNAL USE ONLY**

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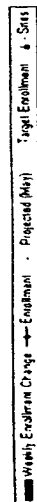
**ABT-773**

## Ongoing Clinical Studies

### Major Findings:

Currently enrolling

Currently enrolling



9 of 10

**HIGHLY CONFIDENTIAL -- FOR INTERNAL USE ONLY**



**July 2001****ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)**Protocol:****Objective:****ABT-773 Doses:****Comparator Doses:****Target Enrollment:****Status:****Major Findings:****M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID**

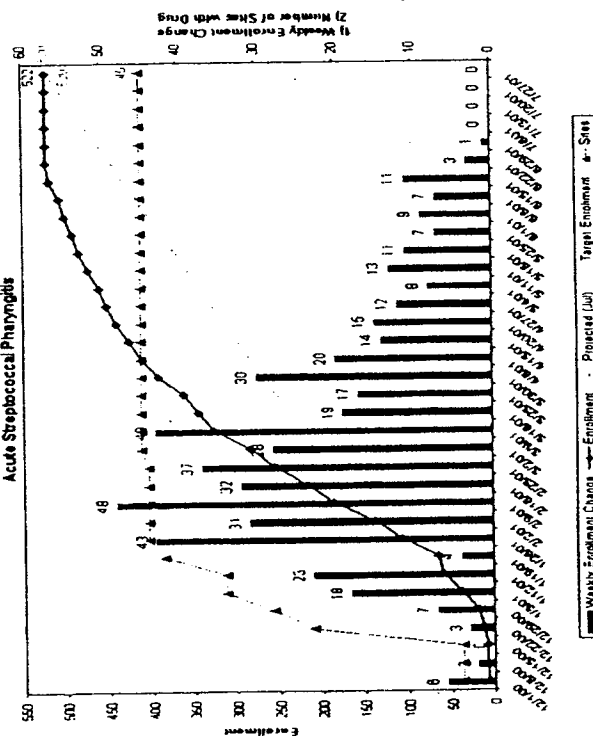
Safety &amp; Efficacy

150mg QD., 5days

Penicillin 500 mg TID, 10 days

520

Currently enrolling

**M00-223 ASP Study (U.S. Sites)  
Acute Streptococcal Pharyngitis****M00-222 - Phase III Pharyngitis vs Penicillin 500mg TID**

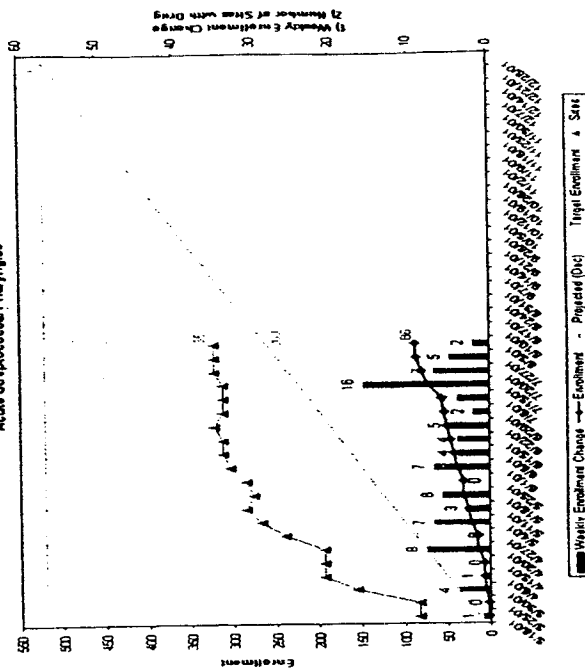
Safety &amp; Efficacy

150mg QD, 5 days

Penicillin 500mg TID, 10 days

520

Currently enrolling

**M00-222 ASP Study (Ex-U.S. Sites)  
Acute Streptococcal Pharyngitis**

D:\77Z\MP\SRs\ABT 773-July01.doc

10 of 10

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From: Eugene Sun  
Stan Bukofzer

INTEROFFICE CORRESPONDENCE

TO: Miles White

Date: Jan. 7, 2002

CC: Jeff Leiden  
John Leonard  
Bill Dempsey  
Dave Goffredo  
Mary Szela  
Jim Tyree

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**RE:**

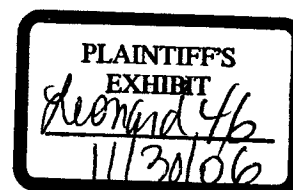
On December 10<sup>th</sup>, the Pharmaceutical Executive Committee met to review the development status of ABT-773, our ketolide antibiotic in clinical development for respiratory tract infections. Based on the data reviewed at the meeting, the Committee recommends suspending further development and initiating efforts to out license the compound. Attached is a package, which addresses the key issues. Our decision for this recommendation is based on the following:

**1. Divergence from the target product profile**

ABT-773 was approved for clinical development in a March 1997 Drug Development Committee (PPCC), at which time the key elements of the target product profile were defined as:

- ◆ Once daily dosing for short course treatment regimens (5-10 days)
- ◆ Favorable side effect profile relative to currently available therapies
- ◆ Efficacy against major respiratory pathogens, particularly against resistant organisms, a key differentiating feature of this compound
- ◆ Once daily dosing has not been achieved in 3 of 4 respiratory indications:
  - ◆ In July 2001, twice daily dosing was chosen for the pivotal Phase III clinical trials in sinusitis and community acquired pneumonia. This decision was taken based on accumulated scientific data and to enhance regulatory approvability of the compound, but recognized a corresponding decrease in the commercial value; particularly given the global trend toward once-a-day/shorter course therapy.
  - ◆ In November, the pivotal U.S. Phase III trial in pharyngitis showed that ABT-773 dosed once daily at the chosen dose had insufficient efficacy for approval. Additionally, these results cast some doubt on the potential for QD dosing for bronchitis.

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ABBT207773

- ◆ The emerging side effect profile of ABT-773 is neither significantly better nor worse than clarithromycin in terms of taste and the potential for drug-drug interactions. There are still safety issues that remain to be better defined, i.e., the potential for QT prolongation, and the incidence and severity of liver enzyme abnormalities (see #3 below).
- ◆ A resistance claim, which is a key point of commercial differentiation, will be challenging to achieve:
  - ◆ The resistance claim is based on successful treatment of pneumonia patients who have resistant organisms. The original ABT-773 plan targeted approximately 15 such patients. In 2001, the EMEA and FDA evaluated telithromycin (Ketek), Aventis' first-in-class ketolide. Neither the EMEA nor FDA considered the Ketek data sufficient to support a resistance claim based on 17 patients with about an 85% eradication rate. It is now anticipated that a resistance claim for ABT-773 will require a larger number of resistant isolates (this requirement will significantly increase the size, complexity, and duration of clinical trials) as well as an eradication rate of at least 85%.
- 2. **Increasing regulatory stringency**
  - ◆ Regulatory approval of new antibiotics is increasingly dependent on their benefit:risk ratio compared to currently available therapies. Given that most respiratory antibiotics have greater than 85% success rates there is increasing attention to drug safety. Although Ketek was approved by EMEA this year, significant post approval commitments were mandated, i.e., additional safety data in over 4000 patients. In the US, Aventis has been asked to obtain additional safety data prior to FDA approval. Given that some of the same safety issues may apply to ABT-773, the projected size of the required safety database for ABT-773 has increased considerably. This will increase the expense and duration of the phase III trials.
  - ◆ Regulatory authorities are increasingly concerned about widespread antibiotic resistance resulting from inappropriate antibiotic usage. They are considering ways to curb indiscriminate antibiotic usage, such as limiting regulatory approval for indications which do not always warrant antibiotic therapy, e.g., acute exacerbation of chronic bronchitis. This indication represents one of the largest respiratory market segments.
- 3. **Unresolved potential safety issues**
  - ◆ QT prolongation by ABT-773 has not been fully characterized and remains a potential liability. In recent years, broad regulatory attention to this issue has resulted in increasing requirements for *in vitro* as well as clinical data to assess this risk. To date, data indicates that QT prolongation by ABT-773 is comparable to that of clarithromycin and Ketek, but FDA has requested additional studies. Should these studies suggest clinically significant risk, regulatory actions could include non-approval, Black Box warning, or contraindication in at-risk populations.

- ◆ Significant liver enzyme elevations have been observed in a few subjects in clinical trials to date, most recently in a study to evaluate QT prolongation. Clinical protocols have been modified to increase patient monitoring, leading to increased clinical costs and a delay in filing. Although the incidence and severity of these findings fall within an acceptable range for antibiotics, future findings may drive the requirement for a larger safety database.
- 4. **Decreased commercial valuation**
  - ◆ The loss of the pharyngitis indication is forecasted to erode more than \$117MM in NPV from ABT-773 (-\$82MM AI; -\$35MM PPD). Based on the above information, the global NPV of ABT-773 falls from a July 2001 \$223MM to \$51MM with the U.S. market NPV largely break-even at \$3MM and Abbott International contributing the balance of value.
  - ◆ In addition, if the regulatory authorities require additional patients to evaluate safety, the value of ABT-773 becomes negative.

Attached are several slides that provide additional detail to the issues discussed above. Obviously we are extremely disappointed to recommend stopping a key phase III program in development. However, at this time, the team recommends placing development on hold and redirecting R & D funds to higher return opportunities. If this decision is made shortly, the team forecasts that it would create a 2002 R&D favorability of approximately \$47MM.

#### **Next Steps**

We look forward to meet with you regarding our recommendation and to secure your approval to move forward with the decision to place clinical development on hold. If approved, the next steps will include:

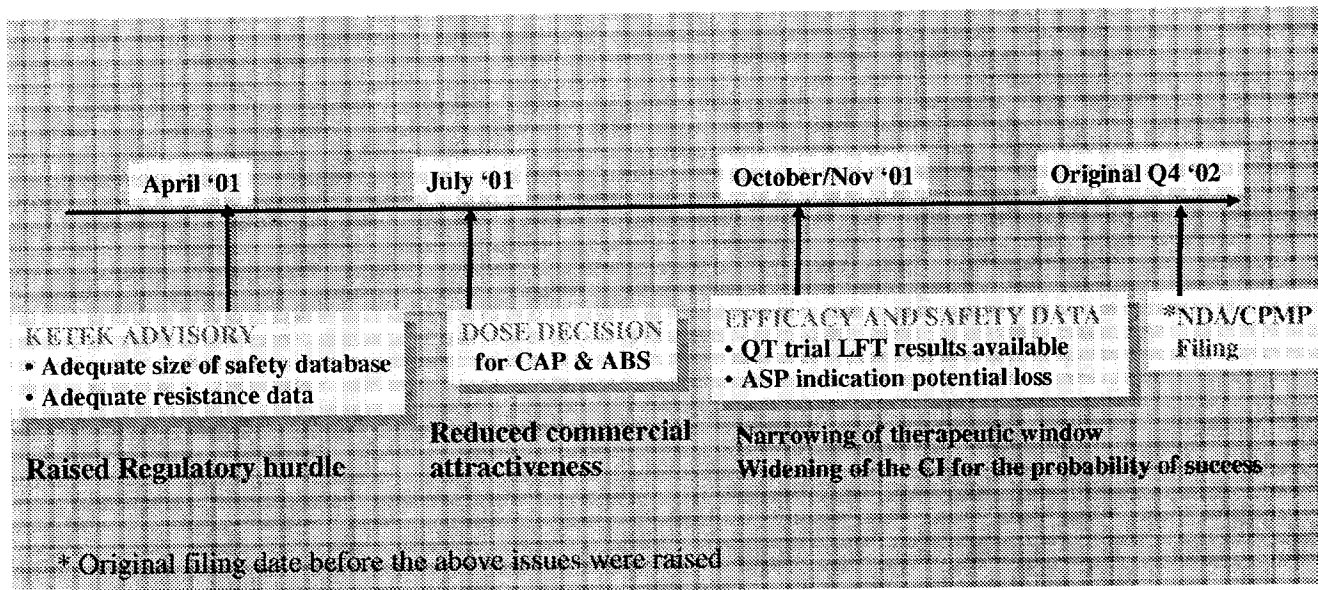
- ◆ The preparation of an internal and external communication package for all stakeholders paying particular attention to PR issues and timing of the process.
- ◆ Communicating with Taisho. As you are aware, the development of ABT-773 has been conducted in collaboration with Taisho under a 1997 Agreement in which Taisho contributes 50% of the Japanese development cost and 10.69% of the ex-Japan expenses. Abbott has the right to out license the compound outside Japan without Taisho's consent, but the royalty obligations remain in effect (5.5% in patented territories and 2.75% in non-patented countries). Sub-licensing of Abbott's rights in Japan is allowed only after Taisho's consent.
- ◆ The PEC believes that the compound may hold potential for out licensing. To capture value for ABT-773 an out licensing effort, which might include follow-on compounds already in discovery, would be aggressively initiated.



Slide 1

**Since the April PEC, the development plan has been impacted by:**

- The Ketek (Aventis) advisory defined the minimum safety and resistance databases for Ketolide anti-infectives
- The BID dosing at variance with market trend to short course once daily therapy
- Loss of pharyngitis indication impacts program financially and has regulatory impact
- The drug is still technically approvable with cost and time penalties, but commercial attractiveness has decreased substantially



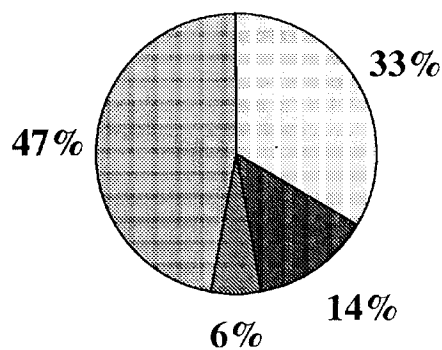
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ABBT220661

Slide 2

**By losing the pharyngitis indication ABT-773 is left to compete in 53% of the adult global respiratory anti-infective market.**

**Global Respiratory Anti-infective Prescriptions by Indication**



**■ Bronchitis ■ Sinusitis ■ Pneumonia ■ Pharyngitis**

Worldwide Antibiotic Market is \$4.85 Billion (IMS Q4 '01)

Note :This includes paediatric and all other indications



Slide 4

**773 has diverged from the original product profile**

- No pharyngitis indication, no pediatric development plan (otitis media)
- No QD dosing for all indications, leaving only bronchitis as a potential QD indication
- Safety – QT interval prolongation liability remains unknown; liver function abnormalities

	March 1997 Target Profile at DDC	December 2001 PEC Review
<b>Clinical Indications</b>		
Bronchitis	✓✓✓	✓?
Pharyngitis	✓✓✓	NO
Pneumonia	✓✓✓	✓✓
Sinusitis	✓✓	✓✓
Otitis Media	✓✓	?
<b>Dosing</b>		
QD Dosing All Indications	✓✓	Bronchitis Only
QD Dosing All Tablet Opportunity	✓✓	Bronchitis Only
<b>Efficacy and Activity</b>		
<i>H Flu</i> Equal to Azithromycin	✓✓✓	✓✓
Atypical Pathogens	✓✓✓	✓✓
Macrolide – Resistant <i>S. Pneumo</i>	✓✓	?
<b>Side Effects</b>		
Low Incident Drug Interactions; Better than Clari	✓✓	NO
Less Metallic Taste than Clari	✓✓	NO
<b>No Serious Adverse Events</b>		
No Significant Liver Elevations	✓✓	?
No Significant QT Prolongation	✓✓	?

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Slide 5

**ABT 773 Profile vs Competitors**

Current ABT 773 targeted profile is inferior to on market products in QD dosing, and is at parity in length of therapy. Obtaining a resistance claim is critical for commercial success, but yields parity to Levaquin. Safety issues surrounding QT interval prolongation and elevated liver function are potential liabilities

Attribute	ABT 773	Clari	Levo	Azi	Ketek
<b>QD dosing</b>	Bronchitis QD No Pharyngitis Pneumonia BID Sinusitis BID	All QD	All QD	All No Sinusitis	All QD
<b>Short-duration therapy</b>	Bronchitis 5 days Pharyngitis N/A Pneumonia 10 days Sinusitis 10 days	Bronchitis 5 days Pharyngitis 10 days Pneumonia 7-10 days Sinusitis 10-14 days	Bronchitis 7 days Pharyngitis N/A Pneumonia 7-14 days Sinusitis 10-14 days	All 5 days or less	Bronchitis 5 days Pharyngitis 5 days Pneumonia 7-10 days Sinusitis 5 days
<b>Resistance Claim</b>	Pursuing	None	Granted (15/15 isolates) (6/6 bacteremic patients treated)	None	Inadequate (14/17 isolates) (4/6 bacteremic patients treated)
<b>Safety</b>	QT, liver to be evaluated	QT and liver liabilities,	No safety issues	No safety issues	QT /liver concerns

Slide 6

**The bacteriological cure rate for ABT 773 was statistically inferior to common penicillin therapy in pharyngitis. In addition, it fails to meet regulatory approval requirements**

*US Pharyngitis Study - Eradication Rate at Test-of-Cure Visit*

<u><b>Bacteriological Eradication</b></u>	<u><b>ABT-773</b></u>	<u><b>Penicillin</b></u>
Per Protocol	74% (140/189)	90% (170/189)
Intent to Treat	64% (141/220)	81% (171/212)
<u><b>Clinical Cure</b></u>		
Per Protocol	85% (160/188)	93% (175/188)

Slide 7

**QT liability still undetermined. Ketek QT was of significant concern to FDA raising possibility of Class effect. To date analysis of the ABT 773 QT data suggests that the QT effect approximates that of Biaxin**

- ABT 773 preclinical data suggests QT prolongation approximating clarithromycin
- To date over 6500 EKG's performed on 1900 patients in ABT 773 program ( Phase 1 & 2)
- Dedicated Phase I QT evaluation study ( 68 patients) with time matched EKG's and serum levels of the drug generating another approximately 10000 EKG's .
- 2 further potential studies in high risk groups ( elderly and cardiac disease) are likely to be FDA mandated
- Phase 3 EKG's with time matched serum drug levels requested by FDA in all Phase 3 studies

**Note : Until agencies assess data at the time of filing, we are not able to know their opinion of the risk**

Slide 8

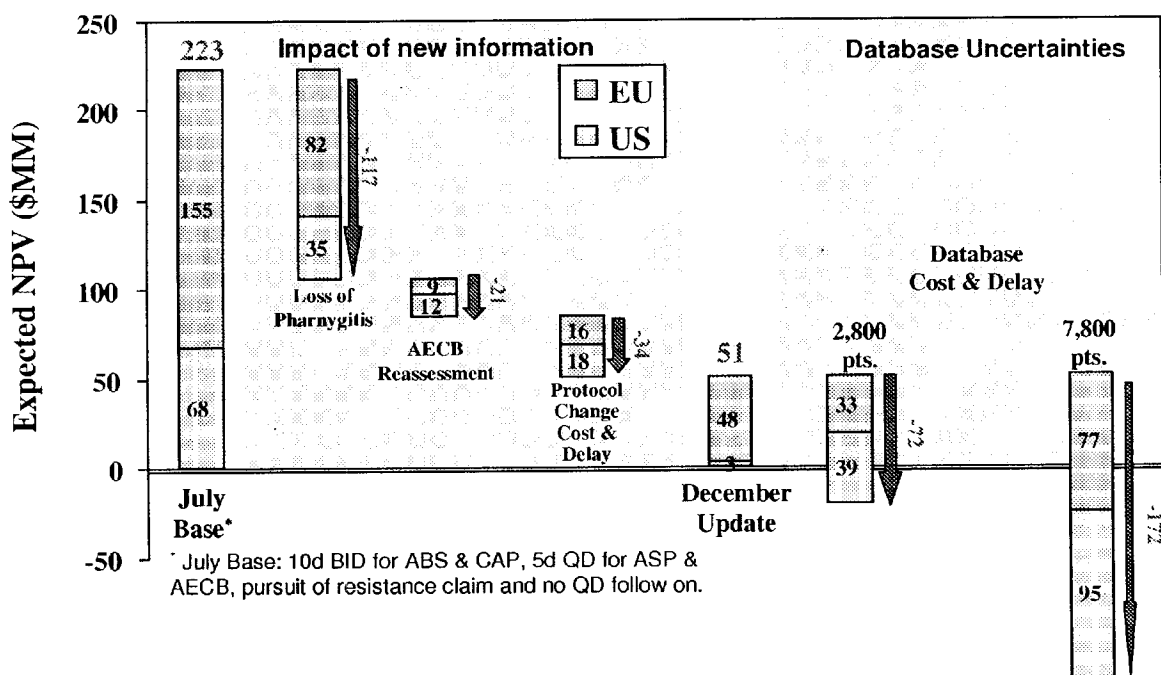
**Complete analysis of liver function tests of entire database revealed no significant case of liver toxicity. However, a finding of a single case in the future could drive database requirement of up to 10,000 patients**

- Definite drug effect with possible greater risk in older individuals and higher doses (over three times maximum dose) has been noted.
- Number of patients with  $\geq 3x$  elevated liver functions is within common limits for antibiotics at at proposed drug doses (includes phase 3 trials) (CDER-PhRMA-AASLD conference Nov 2000)
- No single patient case to date with symptomatic, non-reversible, chronic disease, or significant jaundice (Ketek had two such cases)

### The failure of the pharyngitis pivotal results in a significant value reduction for the ABT 773 tablet project

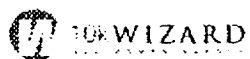
Slide 3

- The probability of obtaining a 5d QD bronchitis indication is lower due to the failure of QD pharyngitis.
- The cost and time impact of changes to the clinical protocols due to LFT concerns results in an additional loss of value.
- If we are required to increase the patient safety database, the remaining value is lost.



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ABBT22067



# FORM 8-K

**Advanced Life Sciences Holdings, Inc. – ADLS**

**Filed: June 25, 2007 (period: June 21, 2007)**

Report of unscheduled material events or corporate changes.

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Item 8.01 Other Events.

Item 9.01. Financial Statements and Exhibits.

SIGNATURES

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EX-99.1 (EX-99.1)



**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**FORM 8-K**

**CURRENT REPORT**

**Pursuant to Section 13 or 15(d) of  
the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): June 21, 2007**

**ADVANCED LIFE SCIENCES HOLDINGS, INC.**

(Exact name of registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction  
of incorporation)

**000-51436**  
(Commission  
File Number)

**30-0296543**  
(I.R.S. Employer  
Identification No.)

**1440 Davey Road**  
**Woodridge, Illinois**  
(Address of principal executive offices)

**60517**  
(Zip Code)

**(630) 739-6744**  
(Registrant's telephone number, including area code)

**N/A**  
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- ☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- ☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- ☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- ☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

**Item 8.01 Other Events.**

On June 21, 2007, Advanced Life Sciences Holdings, Inc. filed a press release announcing results from Trial CL-06, the first of two pivotal Phase 3 clinical trials designed to assess the safety and effectiveness of cethromycin, a novel once-a-day antibiotic, for the treatment of community acquired pneumonia. A copy of the press release is attached hereto as Exhibit 99.1

**Item 9.01. Financial Statements and Exhibits.**

**(d) Exhibits:**

99.1 Press Release dated June 21, 2007.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized

ADVANCED LIFE SCIENCES HOLDINGS, INC.

Dated: June 25, 2007

By: /s/ Michael T. Flavin  
Name: Michael T. Flavin, Ph.D.  
Title: Chairman and Chief Executive Officer

Exhibit Index

Exhibit No.	Description
99.1	Press Release dated June 21, 2007.
	4

Exhibit 99.1

**ADVANCED LIFE SCIENCES**

1440 Davey Road  
Woodridge, Ill. 60517  
(Phone) 630.739.6744  
(Fax) 630.739.6754  
www.advancedlifesciences.com

**FOR IMMEDIATE RELEASE**  
June 21, 2007

Media Contact: Loretta Lepore 404-527-4175  
Investor Relations Contact: Joe Camp 630-754-4352

**Cethromycin Achieves Primary Endpoint  
in Pivotal Phase 3 Pneumonia Clinical Trial**

**CHICAGO, IL, June 21, 2007/PRNewswire/** — Advanced Life Sciences Holdings, Inc. (Nasdaq: ADLS), today announced positive results from Trial CL-06, the first of two pivotal Phase 3 clinical trials designed to assess the safety and effectiveness of cethromycin, a novel once-a-day antibiotic, for the treatment of community acquired pneumonia (CAP). In the study, cethromycin achieved non-inferiority in its primary endpoint of per protocol clinical cure rate compared to Biaxin® (clarithromycin) in CAP. Cethromycin was evaluated using a 300 mg once-daily dosing regimen compared to 250 mg twice-daily dosing for Biaxin®, both over a seven-day course of therapy. Cethromycin also demonstrated safety results that were similar to those seen with Biaxin®.

"We are pleased with the positive results from Trial CL-06 and we believe the strong clinical cure rates coupled with the favorable safety profile seen with cethromycin in this study validate our dosing strategy and will allow us to continue on our current regulatory and commercial partnering pathway," said Dr. Michael T. Flavin, chief executive officer. "Non-inferiority was achieved despite the unusually high clinical cure rate observed with the comparator drug." Dr. Flavin added "We are currently compiling the results from Trial CL-05, our second Phase 3 trial, and we will report top-line results when they are available."

**Study Details**

Trial CL-06 was a multi-center, multi-national, double-blind, randomized, comparator Phase 3 clinical study in which cethromycin was compared to Biaxin® in treating mild-to-moderate CAP. In the study, 522 adult patients were enrolled from clinics in Europe, South America and Israel.

In the study, cethromycin achieved non-inferiority in its primary endpoint of per protocol clinical cure rate compared to Biaxin® in CAP (cethromycin 91.5% (205/224) compared to Biaxin® 95.9% (212/221) [-9.1, +0.3], p=0.0775). Cethromycin's achievement of a 91.5% clinical cure rate is consistent with its Phase 2 clinical trial results at the same 300 mg once-daily dose for CAP. The comparator drug, Biaxin®, achieved a cure rate higher than the historical rate observed in any reported Biaxin® CAP clinical trials to date.

**-MORE-**

Cethromycin also achieved positive safety results in the study. Cethromycin demonstrated an improved safety profile when compared with the results seen in its previous clinical trials. Additionally, the incidence of adverse events was not statistically different between cethromycin and Biaxin®. The most common adverse events reported in patients receiving cethromycin were mild-to-moderate diarrhea (cethromycin 5.0%, Biaxin® 4.6%), headache (cethromycin 3.1%, Biaxin® 6.5%), nausea (cethromycin 2.7%, Biaxin® 3.8%), vomiting (cethromycin 2.7%, Biaxin® 1.5%), abdominal pain (cethromycin 1.5%, Biaxin® 3.1%) and taste disturbance (cethromycin 11.1%, Biaxin® 6.2%). No drug-related serious adverse events were observed in any study subject. Liver function tests and electrocardiogram monitoring demonstrated no significant differences between subjects receiving cethromycin and subjects receiving Biaxin®, consistent with the hepatic and cardiac side effect profile reported in cethromycin's previous clinical trials.

Cethromycin is not approved as a treatment for CAP, and data from this analysis have not been reviewed by the FDA. No further details of the clinical study will be available until all data analyses are complete and results are presented in a public, scientific forum.

#### **Program Design**

The Phase 3 CAP clinical trial program is comprised of two randomized, well controlled, double-blind, multi-center, multi-national, comparator trials designed to assess the safety and effectiveness of cethromycin in CAP patients compared to Biaxin®. Trial CL-06 enrolled patients from clinics in Europe, South America and Israel and Trial CL-05 has enrolled patients from North America and South Africa. Cethromycin was evaluated using a 300 mg once-daily dosing regimen compared to 250 mg twice-daily dosing for Biaxin®, both over a seven-day course of therapy. Biaxin® is an FDA-approved macrolide antibiotic currently indicated for the treatment of CAP.

The primary endpoint for both trials is the clinical cure rate at the test-of-cure visit (Day 14-21 post-initiation of dosing). The eligibility of patients for each trial was based on clinical signs and symptoms and chest X-ray as evaluated by an independent radiologist. Extensive electrocardiogram and liver function test monitoring were incorporated into the study design to examine safety in these areas, and to build on the safety database established in previous cethromycin clinical trials.

Each trial was powered to demonstrate non-inferiority at the 95% confidence interval. To achieve non-inferiority a drug must show that it does not statistically perform any worse than the comparator treatment.

#### **About Community Acquired Pneumonia (CAP)**

CAP is the sixth most common cause of death in the United States. CAP and other respiratory tract infections are caused by pathogens such as *Streptococcus pneumoniae* and *Haemophilus*

-MORE-

*influenzae*. CAP affects 5–6 million patients in the United States each year, with 10 million physician visits and 2 million hospitalizations occurring annually.

Macrolides and penicillins are currently the first-line treatments for respiratory tract infections such as CAP. As macrolide and penicillin resistance grows and has the potential to cause more clinical failures, there is a need for new antibiotics with unique mechanisms of action which can overcome this emerging resistance.

#### About Cethromycin

Cethromycin has shown higher *in vitro* potency and a broader range of activity than macrolides against Gram-positive bacteria associated with respiratory tract infections, and, again in *in vitro* tests, it appears to be effective against penicillin- and macrolide-resistant bacteria. Cethromycin has a mechanism of action that may slow the onset of future bacterial resistance. In addition to its utility in CAP, cethromycin has also been shown to be effective in animal studies for the prophylactic treatment of inhalation anthrax post exposure. The FDA has designated cethromycin as an orphan drug for the prophylactic treatment of inhalation anthrax post exposure, but the FDA has not yet approved the drug for marketing in this or any other indication.

#### About Advanced Life Sciences

Advanced Life Sciences is a biopharmaceutical company engaged in the discovery, development and commercialization of novel drugs in the therapeutic areas of infection, cancer and inflammation. The Company's lead candidate, cethromycin, is a novel once-a-day antibiotic in late-stage clinical development for the treatment of respiratory tract infections including CAP. For more information, please visit us on the web at [www.advancedlifesciences.com](http://www.advancedlifesciences.com).

#### Forward-Looking Statements

Any statements contained in this press release that relate to future plans, events or performance are forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are subject to a number of risks and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. These risks and uncertainties include, among others, those relating to technology and product development, clinical trials, market acceptance, government regulation and regulatory approval processes, intellectual property rights and litigation, dependence on collaborative relationships, ability to obtain financing, competitive products, industry trends and other risks identified in Advanced Life Sciences' filings with the Securities and Exchange Commission. Advanced Life Sciences undertakes no obligation to update or alter these forward-looking statements as a result of new information, future events or otherwise.

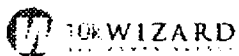
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**732**





# **FORM 8-K**

**Advanced Life Sciences Holdings, Inc. – ADLS**

**Filed: June 25, 2007 (period: June 21, 2007)**

Report of unscheduled material events or corporate changes.

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Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- ☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- ☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- ☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- ☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

**Item 8.01 Other Events.**

On June 21, 2007, Advanced Life Sciences Holdings, Inc. filed a press release announcing results from Trial CL-06, the first of two pivotal Phase 3 clinical trials designed to assess the safety and effectiveness of cethromycin, a novel once-a-day antibiotic, for the treatment of community acquired pneumonia. A copy of the press release is attached hereto as Exhibit 99.1

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits:

99.1 Press Release dated June 21, 2007.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ADVANCED LIFE SCIENCES HOLDINGS, INC.

Dated: June 25, 2007

By: /s/ Michael T. Flavin  
Name: Michael T. Flavin, Ph.D.  
Title: Chairman and Chief Executive Officer

Exhibit Index

<u>Exhibit No.</u>	<u>Description</u>
99.1	Press Release dated June 21, 2007.

Exhibit 99.1

ADVANCED LIFE SCIENCES

1440 Davey Road  
Woodridge, Ill. 60517  
(Phone) 630.739.6744  
(Fax) 630.739.6754

www.advancedlifesciences.com

FOR IMMEDIATE RELEASE

June 21, 2007

Media Contact: Loretta Lepore 404-527-4175

Investor Relations Contact: Joe Camp 630-754-4352

Cethromycin Achieves Primary Endpoint  
in Pivotal Phase 3 Pneumonia Clinical Trial

CHICAGO, IL, June 21, 2007/PRNewswire/ — Advanced Life Sciences Holdings, Inc. (Nasdaq: ADLS), today announced positive results from Trial CL-06, the first of two pivotal Phase 3 clinical trials designed to assess the safety and effectiveness of cethromycin, a novel once-a-day antibiotic, for the treatment of community acquired pneumonia (CAP). In the study, cethromycin achieved non-inferiority in its primary endpoint of per protocol clinical cure rate compared to Biaxin® (clarithromycin) in CAP. Cethromycin was evaluated using a 300 mg once-daily dosing regimen compared to 250 mg twice-daily dosing for Biaxin®, both over a seven-day course of therapy. Cethromycin also demonstrated safety results that were similar to those seen with Biaxin®.

"We are pleased with the positive results from Trial CL-06 and we believe the strong clinical cure rates coupled with the favorable safety profile seen with cethromycin in this study validate our dosing strategy and will allow us to continue on our current regulatory and commercial partnering pathway," said Dr. Michael T. Flavin, chief executive officer. "Non-inferiority was achieved despite the unusually high clinical cure rate observed with the comparator drug." Dr. Flavin added "We are currently compiling the results from Trial CL-05, our second Phase 3 trial, and we will report top-line results when they are available."

**Study Details**

Trial CL-06 was a multi-center, multi-national, double-blind, randomized, comparator Phase 3 clinical study in which cethromycin was compared to Biaxin® in treating mild-to-moderate CAP. In the study, 522 adult patients were enrolled from clinics in Europe, South America and Israel.

In the study, cethromycin achieved non-inferiority in its primary endpoint of per protocol clinical cure rate compared to Biaxin® in CAP (cethromycin 91.5% (205/224) compared to Biaxin® 95.9% (212/221) [-9.1, +0.3], p=0.0775). Cethromycin's achievement of a 91.5% clinical cure rate is consistent with its Phase 2 clinical trial results at the same 300 mg once-daily dose for CAP. The comparator drug, Biaxin®, achieved a cure rate higher than the historical rate observed in any reported Biaxin® CAP clinical trials to date.

-MORE-

Cethromycin also achieved positive safety results in the study. Cethromycin demonstrated an improved safety profile when compared with the results seen in its previous clinical trials. Additionally, the incidence of adverse events was not statistically different between cethromycin and Biaxin®. The most common adverse events reported in patients receiving cethromycin were mild-to-moderate diarrhea (cethromycin 5.0%, Biaxin® 4.6%), headache (cethromycin 3.1%, Biaxin® 6.5%), nausea (cethromycin 2.7%, Biaxin® 3.8%), vomiting (cethromycin 2.7%, Biaxin® 1.5%), abdominal pain (cethromycin 1.5%, Biaxin® 3.1%) and taste disturbance (cethromycin 11.1%, Biaxin® 6.2%). No drug-related serious adverse events were observed in any study subject. Liver function tests and electrocardiogram monitoring demonstrated no significant differences between subjects receiving cethromycin and subjects receiving Biaxin®, consistent with the hepatic and cardiac side effect profile reported in cethromycin's previous clinical trials.

Cethromycin is not approved as a treatment for CAP, and data from this analysis have not been reviewed by the FDA. No further details of the clinical study will be available until all data analyses are complete and results are presented in a public, scientific forum.

#### **Program Design**

The Phase 3 CAP clinical trial program is comprised of two randomized, well controlled, double-blind, multi-center, multi-national, comparator trials designed to assess the safety and effectiveness of cethromycin in CAP patients compared to Biaxin®. Trial CL-06 enrolled patients from clinics in Europe, South America and Israel and Trial CL-05 has enrolled patients from North America and South Africa. Cethromycin was evaluated using a 300 mg once-daily dosing regimen compared to 250 mg twice-daily dosing for Biaxin®, both over a seven-day course of therapy. Biaxin® is an FDA-approved macrolide antibiotic currently indicated for the treatment of CAP.

The primary endpoint for both trials is the clinical cure rate at the test-of-cure visit (Day 14-21 post-initiation of dosing). The eligibility of patients for each trial was based on clinical signs and symptoms and chest X-ray as evaluated by an independent radiologist. Extensive electrocardiogram and liver function test monitoring were incorporated into the study design to examine safety in these areas, and to build on the safety database established in previous cethromycin clinical trials.

Each trial was powered to demonstrate non-inferiority at the 95% confidence interval. To achieve non-inferiority a drug must show that it does not statistically perform any worse than the comparator treatment.

#### **About Community Acquired Pneumonia (CAP)**

CAP is the sixth most common cause of death in the United States. CAP and other respiratory tract infections are caused by pathogens such as *Streptococcus pneumoniae* and *Haemophilus*

-MORE-

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*influenzae*. CAP affects 5–6 million patients in the United States each year, with 10 million physician visits and 2 million hospitalizations occurring annually.

Macrolides and penicillins are currently the first-line treatments for respiratory tract infections such as CAP. As macrolide and penicillin resistance grows and has the potential to cause more clinical failures, there is a need for new antibiotics with unique mechanisms of action which can overcome this emerging resistance.

#### About Cethromycin

Cethromycin has shown higher *in vitro* potency and a broader range of activity than macrolides against Gram-positive bacteria associated with respiratory tract infections, and, again in *in vitro* tests, it appears to be effective against penicillin- and macrolide-resistant bacteria. Cethromycin has a mechanism of action that may slow the onset of future bacterial resistance. In addition to its utility in CAP, cethromycin has also been shown to be effective in animal studies for the prophylactic treatment of inhalation anthrax post exposure. The FDA has designated cethromycin as an orphan drug for the prophylactic treatment of inhalation anthrax post exposure, but the FDA has not yet approved the drug for marketing in this or any other indication.

#### About Advanced Life Sciences

Advanced Life Sciences is a biopharmaceutical company engaged in the discovery, development and commercialization of novel drugs in the therapeutic areas of infection, cancer and inflammation. The Company's lead candidate, cethromycin, is a novel once-a-day antibiotic in late-stage clinical development for the treatment of respiratory tract infections including CAP. For more information, please visit us on the web at [www.advancedlifesciences.com](http://www.advancedlifesciences.com).

#### Forward-Looking Statements

Any statements contained in this press release that relate to future plans, events or performance are forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are subject to a number of risks and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. These risks and uncertainties include, among others, those relating to technology and product development, clinical trials, market acceptance, government regulation and regulatory approval processes, intellectual property rights and litigation, dependence on collaborative relationships, ability to obtain financing, competitive products, industry trends and other risks identified in Advanced Life Sciences' filings with the Securities and Exchange Commission. Advanced Life Sciences undertakes no obligation to update or alter these forward-looking statements as a result of new information, future events or otherwise.

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**AC**

Jeanne M Fox  
04/27/01 07:15 AM

To: Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Eugene X  
Sun/LAKE/PPRD/ABBOTT@ABBOTT, Stan  
Bukofzer/LAKE/PPRD/ABBOTT@ABBOTT, Carol S  
Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Lawrence E  
Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Rod M  
Mittag/LAKE/PPD/ABBOTT@ABBOTT, Tim  
Vanbiesen/LAKE/PPRD/ABBOTT@ABBOTT

cc:  
Subject: FYI - Ketek

----- Forwarded by Jeanne M Fox/LAKE/PPRD/ABBOTT on 04/27/2001 07:14 AM -----

## **FDC Reports Pink, Tan, Gray Sheets**



HEALTH-NEWS-DAILY

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HLTHND: Health News Daily

April 26, 2001 Thursday

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### **Aventis' Ketek Needs Additional Safety Data Before Approval For CAP, Cmte Says**

HEALTH-NEWS-DAILY , April 27, 2001, Page 4

Aventis' Ketek (telithromycin) needs additional data on QT prolongation and hepatotoxicity prior to approval for community acquired pneumonia, FDA's Anti-Infectives Advisory Committee said April 26.

The committee recommended in a 7 to 3 vote that FDA approve the antibiotic for community acquired pneumonia, which is one of four indications being sought by the company.

Committee members voted unanimously against approval of Ketek for acute exacerbation of chronic bronchitis. Members questioned whether the benefit of Ketek would outweigh the risk in this population, given the availability of alternative therapies.

The committee also voted 8 to 2 against approval of Ketek for acute sinusitis, citing similar concerns.

The fourth indication Aventis is seeking for Ketek, tonsillitis/pharyngitis, was not addressed by the committee.

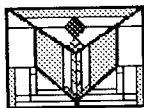
FDA statistician George Rochester, PhD, expressed concern with the risk/benefit ratio of telithromycin for tonsillitis/pharyngitis, noting that it is a mild disease, and the target population is typically children. Aventis' Ketek application includes data in patients 13 and older.

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**AL**



Carol S  
Meyer/LAKE/PPRD/ABBOTT  
09/20/2001 01:29 PM

To: Stan Bukofzer/LAKE/PPRD/ABBOTT  
cc:  
bcc:  
Subject: Re: Portfolio issues update

I made my corrections in red. I only have one more issue to clear up with Bill. The PARD numbers on the detail don't match and I think he has an error in the total cost, but I'll verify and let you know  
Stan Bukofzer



Stan Bukofzer  
09/20/2001 12:27 PM

To: Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: Portfolio issues update

----- Forwarded by Stan Bukofzer/LAKE/PPRD/ABBOTT on 09/20/01 12:27 PM -----



Stan Bukofzer  
09/19/01 12:32 PM

To: John M Leonard/LAKE/PPRD/ABBOTT  
cc:  
Subject: Re: Portfolio issues update

John  
Thanks for the opportunity to address the questions. All answers in Blue.  
Corrections

John M Leonard

John M Leonard  
09/18/01 11:24 PM

To: Stan Bukofzer/LAKE/PPRD/ABBOTT  
cc: Eugene Sun, Kenneth Stiles, Thomas Woidat, Thomas Lyons  
Subject:

In preparation for Friday, I have some questions that follow. You can send answers in advance of the meeting or bring them with you.

Thanks,  
J

ABT-773

(see the "2002 PLAN Development Summary " cover sheet)

Clinical Program -

I assume the accruals for 219 run through 3/02 and not 03  
Yes, this is a typo, should be ending enrollment in 3/02

Of the clinical programs with substantial activity this year, which can have costs accelerated in to 2001?

We can try to accelerate spending in 2001. Dependent on start of patient enrollment

I do not have a grants page . Therefore, can you give me a quick summary of per patient costs of the studies that will be running next year? I am particularly interested in costs per patient by indication by investigator grants as well as CRO costs .



Clinical Grants 2002 9.19.01.x In case you cannot open the project file, the direct CRO costs are approximately \$ 5200 per patient on average for CAP and Sinusitis . Investigator grants vary from \$1700-3600 for sinusitis and \$ 5000-\$1800 for CAP depending on area of world . It is fiercely competitive to recruit these patients and we pay at the lower end of market .

I like the graph describing bulk drug costs . Some text will be helpful to explain it, however . Please mention the ultimate target costs at launch (bulk and then finished product ) . Also, we are spending \$9.8MM on process chemistry, not an inconsequential amount . Please summarize what this is on a sheet to add to the material prepared . Who is working on this, what are they doing, what are the deliverables, and why are we spending so much? What will we do with the material that they produce?



773 bulk drug timeline 9.7.01.PC

Campaigns 17 & 18 are development /engineering runs postponed from 2001 to 2002 based on the revised filing date . Yield is estimated to be 670kg for these 2 campaigns, cost is \$ 2.130M. 400kg of these campaigns will be used to run the Demonstration batch for the US mfg site, AP 16. Also in 2002, Intermediate steps 3-5 will be run in -house or at a vendor to prepare for the Bulk Drug validation runs (4) to be run in 2003, cost is \$ 1,950M. Costs for these intermediates in 2002 will be partially credited back when validation lots are used as part of product for sale . Remaining costs are: \$3,611M for process chemistry headcount to do process justification for the NDA, \$ 1,459M for Analytical support and \$ 427M for Pilot plant and vendor development .

We need more details on formulation and analytical . What is being done for \$ 8MM? I know that we will get stability as part of the answer, but this needs to be explained . Is anyone looking at what the stability program is and how much it costs? Do we really need to do everything that is being done?



PARD 773.xls

The stability program supports the filing strategy of 4 finished product NDA lots on stability to represent all four Vendors supplying step 2 intermediate for bulk drug . This was done to support step 2 as a starting material in case the regulatory agencies did not agree to our step 5 starting material justification . Our stability matrix supports bottle and blister configurations requested by US and AI marketing groups .

Costs for IDC for 2001 to support the U.K. final product scale up activities was \$ 1,791M. This should be reflected in Other CMC costs for 2001 (the Development Cost Summary listed these costs in Other Support Costs incorrectly ). All activities to support the U.K. scale up are transferred to PARC in 2002. These costs are now part of the PARC budget for 2002. Total Tablet Formulation /Analytical budget in 2001 was \$7015M. In 2002 Tablet Formulation /Analytical budget is \$6511. PARC costs for IV are \$ 117M.

I have a problem with costs listed as "other." In Tox, there is \$ 2.2MM and under "other" there is yet another "other" at \$3.2MM. Therefore, "other" on this program totals \$ 5.4MM out of a total of \$77.1MM. We need to pin this down .

Drug Safety "Other" costs consist of Clinical Drug Analysis \$1,690M. In 2002, approx. 20,500 plasma/tissue samples require drug analysis support for Phase I & III studies. Remaining "other" drug safety costs are Drug Metabolism \$302M. These support remaining studies /documentation required for the NDA.

**Other Support Costs :**

"Other" costs include Discovery Structural Chemistry and Pharmacogenetics \$ 635M with activities planned to evaluate genetic differences of Japanese vs western subjects in Phase I /III studies. Microbiology research \$ 2,166M required support for Phase III micro labs isolate testing, Phase III analysis of clinical resistant isolates and remaining micro studies required for NDA.

What is our approach for microbiology grants? We have set aside \$ 2MM. What are we supporting? Who is deciding what to support? What end are we trying to achieve? How many people do we support and what are we paying on a typical grant? What are we doing with the data?

The external study grants are planned to support label claims, NDA requirements and key ABT 773 communications. Studies range in cost from \$ 5,000 to \$200,000 with the average cost at approx. \$30,000. Study designs are in vitro activity, animal PD models, or a combination of both, and post-approval will also manage investigator -run human studies. An External study committee consisting of Venture, Microbiology, New Product development, AI business development and the Franchise Medical liaison (ML) group meets each month to evaluate submitted proposals. Proposals are approved based on the rationale and expected results in support of the ABT 773 filing and marketing strategy. The committee also develops requests to be sent out to Abbott MLs and ex-US Abbott contacts for specific proposals to support label claims, NDA requirements, or key 773 communication plans. Opinion leaders from every region worldwide are being developed to support global filing and marketing activities.

All external studies are submitted, approved, managed and tracked via the ABT 773 Study Tracking website accessed by the Steering committee and all Abbott MLs (with ex-US Abbott contacts planned to access the website by the end of 4Q 2001). All payments and drug shipments for these studies are also managed via this web -site by Venture document specialists. All approved studies are indexed by study content for searching /reporting capabilities. A web-page containing the draft label will be linked to each of the studies used to support the individual label claims. Multi-center studies will also have the appropriate links to the label claims.

I need more detail on venture management> What are we getting for our \$ 6.7MM? how many heads? What is the approach to travel? What money is squirreled away here? Please take me through it because I need to have a sense of what are the soft spots. For the dept. I have worked on 58 heads, but discounted a full 3 salaries to account unfills during the year. Of these 42 are in 773 and 14 in 492. For travel it is zero based and divided it into 3 parts. (1. Dept including some support area travel to congresses, meetings etc, 2. 492 study travel and 3. 773 study travel). I am working on an easy to justify slide because the assumptions used in 773 and 492 were similar, but I cut 773 budget more than 492 given the size of it. Overall however there is little if any fat in this budget since with the exception of headcount and travel, most other accounts in departmental budget have been reduced.

Our RA/QA budget equals \$ 1.3MM. At \$0.15MM/head, we will have 8 FTEs. Do we really have 8FTEs? Remember, an FTE is a Full time equivalent. I doubt that we have more than 1 RA FTE and there is no way that there are 7 QA FTEs on this project. The cost represents 4.83FTE for a cost of \$ 1064.9MM in ToxQA, Clinical compliance, Records and PPD RegAffairs. I have reviewed it from a zero base and it seems very reasonable. ( see 492 answer for more detail )

What does HPD IV development mean? What does this consist of? How do we pay them?



ABT-773 IV 2002 Plan.rtf

HPD costs will be charged through inter-divisional services purchased.

On the page called "Phase III Clinical Plan," it is helpful if you denote somehow those studies already underway.  
Will do so.

Your Japanese development plan flow chart is very helpful.  
Great, it exercised my powerpoint skills considerably!

Please add a page summarizing the QT situation (background and required studies).



773 QT issues summary.doc

What can you do this year on the IV program if additional funding is made available, especially for external expenses?

Unfortunately nothing clinically, as we await the first in man trial to begin and data to be generated before we proceed with further studies. From a formulation point of view....

I am confused by what you show for the PK data in the IV program. What is this data and when (how) was it obtained?

I will label more precisely. The PK data shown on the IV slide is a simulation model based on modelling assuming an absolute bioavailability of 35% and linearity of dose response.

Please add a few words describing the likely IV trail that you intend to do - days therapy and how to step down.

The IV trials consist of the following:

Single rising dose (first in man) followed by a multiple dose study for the phase 1 program. The definitive phase 3 trial proposed (subject to regulatory buy in) is a comparative trial of IV ABT 773 followed by oral ABT 773 against IV ceftriaxone with or without IV erythromycin followed by an oral cephalosporin with or without oral macrolide. The subjects would receive initially IV regimen ranging from a minimum of 3 days to max of 7 days followed by an option to change to the oral regimen for the balance of the treatment; which may range from 3 to 7 days. A total of 750 subjects are anticipated for this kind of study. At present it is unclear whether one global trial would satisfy both EU and FDA requirements or separate US and EU trials will be required.

Please add a few words to the Peds slide on what we believe compliance with the FDA's pediatric



program consists of. (p33 or 115) 773 Pediatric program issues.p

I cannot tell from the slides what is the status of the Ped formulation. Have we selected one? If not, what are we looking for and how are we looking for it?

We have no formulation yet. Two prototypes were not bioequivalent to tabs. Taste testing was done on these and it was better than Clari, but worse than Azi. Following our discussions I have determined that we can start the formulation work in Mid OCT. The purpose is to optimise the granules and the suspension. SWix months later we plan to do the 1st clinical bio study.





Please provide GANT charts for the PEDs and IV programs . IV programgant chart.pp

ABT-492 Attached is a powerpt presentation for budget backup (6 slides)



ABT-492 cost backup.ppt

see PLAN summary page:

My comments from 773 with respect to CMC andTox also apply here .

CMC support represents 500kg of bulk and formulation development of commerical product . More detail of the breakdown of cost are in attached presentation slide 2. A list of Tox studies and cost are on slide 3. These studies are listed in the current IND submitted to the FDA .

The "other" category here is \$ 4.6MM. The ration to the total program is 4.6/43.4, or > 10%!  
The sheets are new to us all and where to put "other" cost is confusing . The Other cost is Drug Safety should be \$ 1.2MM which represents FTE in Drug Analysis needed to support all PK samples being taken in the Phase I and II studies . (see slide 3)  
Other cost in Support is \$ 2.5MM. Of this \$ 2.2MM represents FTE in the Micro (Discovery) area supporting the evaluation of samples in the clinical trials . See slide 4

Please add a few words to describe the milestone payments .

See slide 6

My questions for RA /QA continue here . The total is nearly the same as 773 yet the clinical activity is a fraction of 773. Something is not correct . Have you challenged the QA people to state their auditing program? Do you agree with it?

The cost represents 4.5FTE in RQA, Compliance, Records and RA .and is zero based . There was 1 mistake of 0.06 being entered in 1 area for 1 study instead of 0.006. ie net result is that 492 is over budgeted by 0.5 FTE in R 44J. We have not made any changes at this time . There is a mix difference between the 2 compounds .

ABT-773 G0-202.170			ABT-492 G0-233.270		
	FTEs	\$(000)		FTEs	\$(000)
R42i	1.0	\$ 196.7		0.75	\$ 147.6
R49i	1.0	226.7		0.50	113.3
R44F	0.46	104.3		2.13	482.8
R44J	2.37	537.2		1.68	380.8
Total	4.83	\$ 1064.9		4.31	\$ 1124.5

Once again, for venture management, how many people are we supporting? What else is in here, especially for travel .

2001 support was budgeted for 5 FTE (Ops Mgr, MD, CPM and 2 CRAs). With increase of Phase I and II trials support will increase to 13 (add include 3 CRAs, 2 Doc Clerk, 2 Med. Reviewers and a CPM transferred from 773).

How do travel costs when normalized compare to 773? You could look at it by \$ /patient, \$ /site, or similar approaches . Either way I would like to know what we are doing .

Travel driven by actual number of sites visits for ABT -492

Same micro studies comments as for 773.

*Subsequent pages*

Please lay out the milestone payments . A good place to do it might be on the GANT chart describing the overall program .  
see slide 6

I agree that the LFT map is provocative . Can we provide something similar for Clari for comparison's sake?  
Unfortunately that data would have to be looked for in the databases, so there is a longish lead time on that .

Do you really believe that we are getting enough resolution on the AECB Phase II safety study? I think the confidence bounds are very wide .

For two-sided 95% confidence intervals with 80 subjects we have the following for the AECB protocol:

Rate	CI
10%	(3.4%, 16.6%)
15%	(7.2%, 22.8%)
20%	(11.2%, 28.8%)
25%	(15.5%, 34.5%)
30%	(20.0%, 40.0%)

Note that levofloxacin clinical trial rates of nausea and diarrhea are 7.1% and 5.6%. Therefore, if we observe a 492 rate between 10-15% in the AECB trial for either of these events, it is likely 492 is worse than levo as the lower end of our 95% CI is 7.2% for an observed rate of 15% (even though CIs would likely overlap between 492/levo within the trial even in this case - levo is acting as an internal control to be sure it performs similarly in our study compared to quoted rates).

If the observed AE rates are less than 10% for 492, then we need to look at 75% and 50% CIs and balance risk of uncertainty vs. commercial implications of potential rate of diarrhea shown by upper bound of confidence interval. For example, 75% and 50% CIs around an observed rate of 10% are (6.1%, 13.9%) and (7.7%, 12.3%), respectively. That means that we are 75% sure that our diarrhea rate could be as high as 13.9% and is at least 6.1% and there is an even chance that it could be as high as 12.3%. Adding an additional 20 patients/arm (n=80) total for study did little to significantly tighten these intervals. It comes down to a balance between cost, time to enroll, and precision of our estimates.

Are we really pursuing prostatitis as an indication? (see p.135 for "Continuing Phase I /2a Indications"). Not at present - no phase II studies are being planned - it is merely for safety surveillance .

With respect to the prostatitis work, a picture will be helpful to describe exactly what we think we are investigating . I favor some kind of a distribution curve that indicates the proportion of the population likely to take drug for the duration in the study and then another curve for the proportion of the patient population likely to be exposed at these doses . In other words, I want to illustrate how representative (or unrepresentative) the data will be of what patients will actually receive .

The purpose of the prostatitis trial is to stress the drug with exposure and duration higher than what we expect to see at registrational levels . For example, we do not plan to go beyond 10 days in our planned indications, so no one should get the drug for 28 days except off label, for which it is not possible to predict usage . With regard to exposure, note that a 600 mg dose provides a mean AUC of 25000 ng\*h/mL. The highest value observed in phase 1 for any subject receiving 100, 200, or 400 mg was only 22000 ng\*h/mL, so our AUCs are above what we would expect even at our highest potential clinical dose . However, that is not to say that an elderly patient or one with reduced renal function would not reach these levels, so the 600 mg dose may be acting as a surrogate for exposures for those at risk populations .

The question we need to be able to answer is what signal would lead us to stop development in this noncomparative trial. Note trova had 9% ALT > 3x ULN in their similar prostatitis study. I seem to recall from an FDA presentation that less than 1% of subjects normally have elevations to this level in placebo controlled trials, although I would need to confirm it. The fundamental assumption behind running this study is that our desire for an ultraclean profile is so high that we would stop development if anything questionable was seen here. If this is not our strategy, we should not do the trial as we will have to live with the consequences.

The slides of the various quinolone uses is not readable in black and white.  
Slides on quinolone use have been updated for easier reading in black and white.  
Stan Bukofzer

The pie charts are provocative, but potentially misleading. You should indicate the launch dates for the various drugs. Is the distribution of the uses a reflection of how drugs grow on the marketplace, how they were originally launched, or something else? I would include the total sales with the pie charts.

Changes made on the chart per your request. Distribution of use has shifted since the introduction of gati (Tequin) and moxi (Avelx) in 2000. These drugs have targeted the RTI indications and captured some share from macrolides.

Need more information on the comment about losing a year during the phase 2b program. I do not understand the comment.

For regulatory status, pls add a few words about the contraceptive issues.



I will. Herewith more detail FYI. ABT-492 OC IND update.ppt

The program cost page (p 151) is incomplete.  
Will be corrected

Thanks,

J

John M. Leonard, M.D.  
Vice President  
Global Pharmaceutical Drug Development  
Global Pharmaceutical Research and Development  
PH: (847) 938-4545  
FX: (847) 937-3918



**BS**

Westlaw

6/11/07 CRCHICBUS 4

NewsRoom

Page 1

6/11/07 Crain's Chi. Bus. 4  
2007 WLNR 11271879

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June 11, 2007

Volume 30; Issue 24

Section: Markets

Waiting to exhale

Day of reckoning nears as biotech firm Advanced Life awaits trial results on new treatment for pneumonia

MIKE COLIAS

A local biotechnology company will either be breathing a lot easier in coming weeks, or it may be near its last gasp.

Advanced Life Sciences Holdings Inc. is counting on favorable results later this month from a 1,000-patient clinical trial on Cethromycin, an antibiotic the Woodridge company is developing to treat pneumonia. Success may ultimately pave the way to a \$500-million-a-year hit, analysts say. Failure could be fatal as Advanced Life, which has yet to post a profit in its eight years of existence, has no other drugs even close to market.

The company "really needs a positive result to continue to exist," says Angela Larson, an analyst with New York-based Susquehanna Financial Group.

Investors optimistic

Investors, betting that Cethromycin will pass muster, have sent shares of Advanced Life up 27% so far this year. The stock ended last week at \$3.46, giving the company a market value of \$98 million. Ms. Larson rates the stock the equivalent of a "buy."

Cethromycin targets "community acquired" pneumonia: Distinct from the strain of the illness patients catch in hospitals, it's the sixth-leading cause of death in the United States, with more than 5 million cases a year. Antibiotics on the market fail to work nearly 40% of the time because bacteria have built up resistance to them, so the drug could emerge as a market leader if it wins approval from the U.S. Food and Drug Administration. If the drug passes its trial, analysts expect FDA approval and a product launch by year-end 2008.

Elemer Piros, a New York-based analyst with Rodman & Renshaw LLC, estimates in a report that Cethromycin may eventually reach 25% of the \$2-billion global market for drugs that fight community-acquired pneumonia.

Advanced Life expects to retain up to 30% of Cethromycin sales through royalty payments, with much of the rest going to a marketing partner the company hopes to name later this year, CEO Michael Flavin says.

Abbott stands to benefit

Cethromycin could also provide a nice payday for Abbott Laboratories, which licensed the drug to Advanced Life in 2004. Abbott, Advanced Life's second-largest shareholder with 6.1% of shares outstanding, would get 17% to 19% of total sales

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under the licensing pact. North Chicago-based Abbott also is among the companies angling for the marketing deal, analysts say, which could further boost its payoff. An Abbott spokeswoman declines to comment.

Some other local biotech firms have stumbled with new-drug efforts. Shares of Waukegan-based Neopharm Inc. and Evanston-based Northfield Laboratories Inc. plunged in recent months after each posted poor test results for lead-drug candidates.

A better fate awaits Advanced Life, says Mr. Flavin, who previously led another Woodridge drugmaker, MediChem Life Sciences Inc. In 2002, Mr. Flavin sold MediChem to Iceland-based Decode Genetics Inc. for \$83 million.

Mr. Flavin says Advanced Life could survive poor test results. He points to six other drugs the firm is developing, as well as potential revenue from selling Cethromycin to the U.S. military as an anthrax treatment.

"We believe Cethromycin is a more potent antibiotic than any now on the market," Mr. Flavin says.

Contact: mcolias@crain.com

#### ----- INDEX REFERENCES -----

COMPANY: ABBOTT DIABETES CARE INC; US FOOD AND DRUG ADMINISTRATION; ADVANCED LIFE SCIENCES INC; DECODE GENETICS INC; VYSIS INC; ABBOTT LABORATORIES INC; NORTHFIELD LABORATORIES INC; MEDICHEM LIFE SCIENCES INC; NEOPHARM INC

NEWS SUBJECT: (Forecasts (1FO11); Major Corporations (1MA93); Economics & Trade (1EC26))

INDUSTRY: (Plastics (1PL57); Pharmaceuticals & Biotechnology (1PH13); Chemicals (1CH04); Drugs (1DR89); Medical Plastics (1ME58); Trends in Technology (1TR23); Infection Control & Epidemiology (1IN02); Antibiotics (1AN81); Internal Medicine (1IN54); Polymers (1PO43); Commodity Chemicals (1CO31); Chemicals Regulatory (1CH23); Infectious Diseases (1IN99); Pharmaceuticals Regulatory (1PH03); Medical Devices (1ME31); Science & Engineering (1SC33); Healthcare (1HE06); Healthcare Practice Specialties (1HE49); Respiratory & Pulmonary (1RE29))

REGION: (North America (1NO39); New York (1NE72); Americas (1AM92); USA (1US73))

Language: EN

OTHER INDEXING: (ABBOTT LABORATORIES; ADVANCED LIFE; ADVANCED LIFE SCIENCES HOLDINGS INC; CETHROMYCIN; DECODE GENETICS INC; FDA; MEDICHEM LIFE SCIENCES INC; NEOPHARM INC; NORTHFIELD LABORATORIES INC; RODMAN RENSHAW LLC; US FOOD AND DRUG ADMINISTRATION) (Abbott; An; Angela Larson; Elemer Piro; Flavin; Investors; Larson; Michael Flavin; Waiting)

KEYWORDS: (Economy); (Business and Finance); (Financial and Business Services)

Word Count: 640

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6/29/07 Crain's Chi. Bus. (Abstracts) 4  
2007 WLNP 14625373

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June 29, 2007

Waiting to Exhale.  
Clinical trials.

Colias, Mike.

United States Biotechnology company Advanced Life Sciences Holdings Inc. is counting on favorable results from a clinical trial of Cethromycin, an antibiotic that it is developing for the treatment of pneumonia. Although the eight-year-old company has yet to post a profit, its share price has risen by 27 percent since the start of 2007 because investors believe that Cethromycin will pass its trial and win FDA approval. According to Elemer Piro, a New York-based analyst with Rodman & Renshaw LLC, Cethromycin could eventually reach 25 percent of the \$2-billion global market for drugs that fight community-acquired pneumonia. However, failure could be fatal for the company, as it has no other drugs even close to market.

---- INDEX REFERENCES ----

COMPANY: ADVANCED LIFE SCIENCES INC

INDUSTRY: (Pharmaceuticals & Biotechnology (1PH13); Drug Approval Process (1DR91))

Language: EN

OTHER INDEXING: (ADVANCED LIFE SCIENCES HOLDINGS INC; FDA; RODMAN RENSHAW LLC)  
(Biotechnology; Elemer Piro)

Word Count: 146

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8/21/07 Life Sci. Wkly. 5808  
2007 WLNR 15949147

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August 21, 2007

Section: Expanded Reporting

Reports from Advanced Life Sciences Holdings, Inc., describe recent developments  
Advanced Life Sciences Holdings, Inc.

Reports from Advanced Life Sciences Holdings, Inc., describe recent developments.

This trend article is an immediate alert from NewsRx to identify the most recent news developments at Advanced Life Sciences Holdings, Inc.

Report 1: Advanced Life Sciences Holdings, Inc. (NASDAQ:ADLS), announced positive results from Trial CL-06, the first of two pivotal Phase 3 clinical trials designed to assess the safety and effectiveness of cethromycin, a novel once-a-day antibiotic, for the treatment of community acquired pneumonia (CAP). In the study, cethromycin achieved non-inferiority in its primary endpoint of per protocol clinical cure rate compared to Biaxin(R) (clarithromycin) in CAP. Cethromycin was evaluated using a 300 mg once-daily dosing regimen compared to 250 mg twice-daily dosing for Biaxin(R), both over a seven-day course of therapy. Cethromycin also demonstrated safety results that were similar to those seen with Biaxin(R).

Report 2: Advanced Life Sciences Holdings, Inc. (NASDAQ:ADLS), announced the confirmation of supplemental efficacy data from Trial CL-06, the first of two pivotal Phase 3 clinical trials designed to assess the safety and effectiveness of cethromycin, a novel once-a-day antibiotic, for the treatment of community acquired pneumonia (CAP). The Company also provided an update to the projected timeline for announcement of top-line data from the second CAP study, Trial CL-05.

The Company is hosting a conference call and live webcast at 10:00 am (EDT) today, July 2, 2007 to discuss the available data from Trial CL-06. On the call will be members of the Advanced Life Sciences management team along with Donald E. Low, M.D., a recognized authority in microbiology and infectious diseases.

Report 3: Advanced Life Sciences Holdings, Inc. (NASDAQ:ADLS), announced its financial results for the first quarter ended March 31, 2007. The net loss for the three months ended March 31, 2007 was \$10.4 million or (\$.37) per share compared to \$3.2 million or (\$.15) per share for the three months ended March 31, 2006. The increase in the net loss reflects increased development expenses related to pivotal Phase III clinical trial costs of the Company's novel once-a-day antibiotic, cethromycin.

"Advanced Life Sciences continued to make substantial progress in the first quarter of 2007," said Michael T. Flavin, Ph.D., chairman and chief executive officer of Advanced Life Sciences. "We are nearing the end of our clinical work with cethromycin and are building toward a robust NDA submission. We were pleased to announce last week very positive efficacy data from our non-human primate study in inhalation anthrax. Looking forward, our focus is on the release of top-line data from our pivotal Phase III program in CAP that we expect to occur in June of this year."

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----- INDEX REFERENCES -----

COMPANY: ADVANCED LIFE SCIENCES INC; INNOVATIVE INTERFACES INC

INDUSTRY: (Science & Engineering (ISC33); Drugs (IDR89); Infectious Diseases (IIN99); Pharmaceuticals & Biotechnology (IPH13); Infection Control & Epidemiology (IINO2); Antibiotics (IAN81); Science (ISC89))

REGION: (USA (IUS73); Americas (IAM92); North America (INO39))

Language: EN

OTHER INDEXING: (ADVANCED LIFE SCIENCES; ADVANCED LIFE SCIENCES HOLDINGS INC; CAP; III; NASDAQ:ADLS; NDA) (Donald E. Low; Michael T. Flavin; Report; Trial)

KEYWORDS: Clinical Trial Research; Advanced Life Sciences Holdings Inc

Word Count: 559

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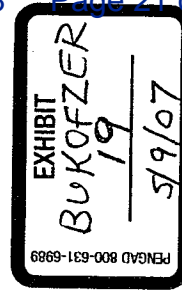
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## ABT 773 Agenda

- Product Profile impacted by:
  - Ketek FDA advisory
  - New Efficacy data
  - New Safety data
- Summary
  - Narrowing of therapeutic window
  - Increase widening of the CI for the probability of success
  - Reducing NPV of the product
- Future options

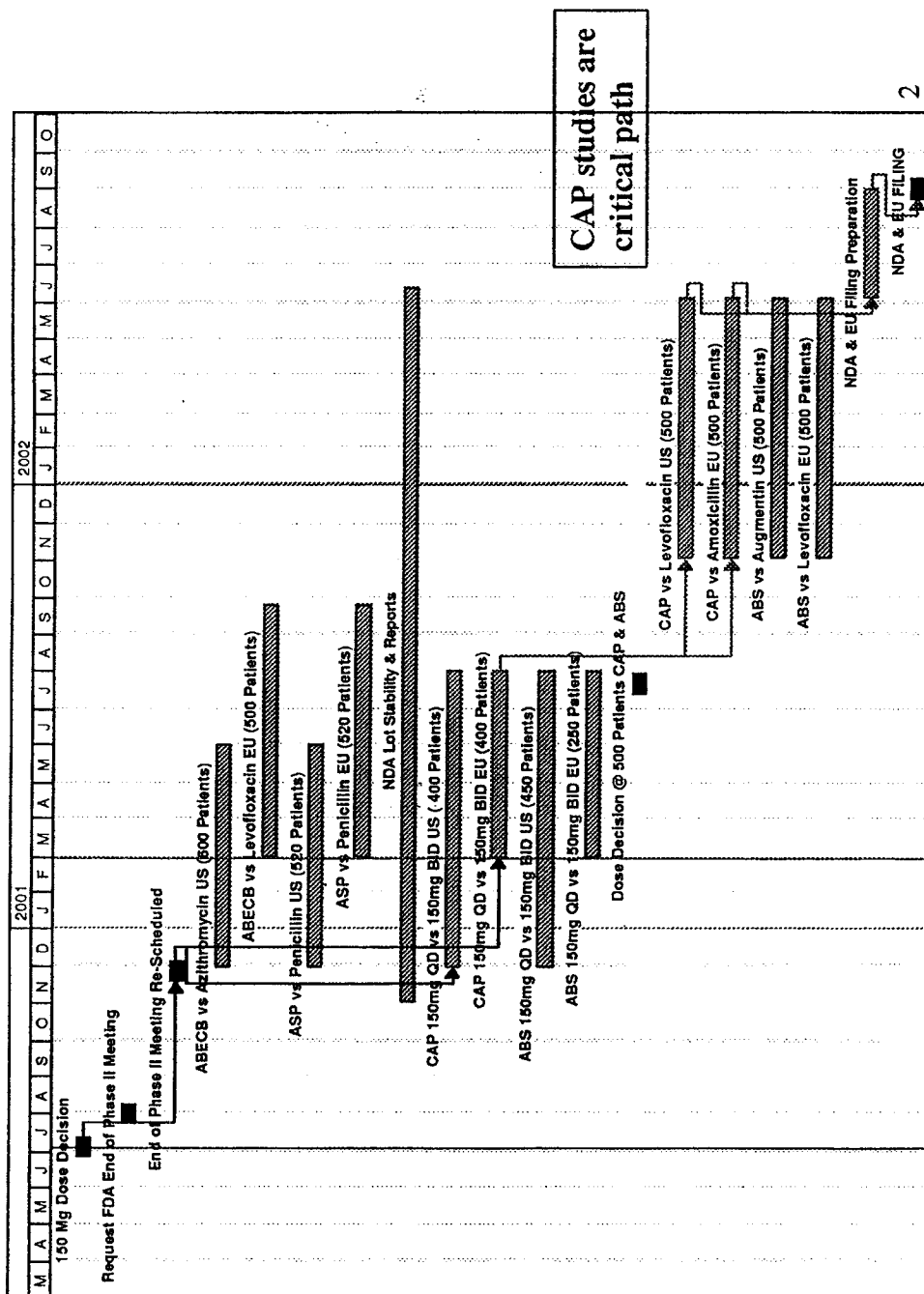
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ABBT271783

# ABT 773 Development Timeline as of March 2001



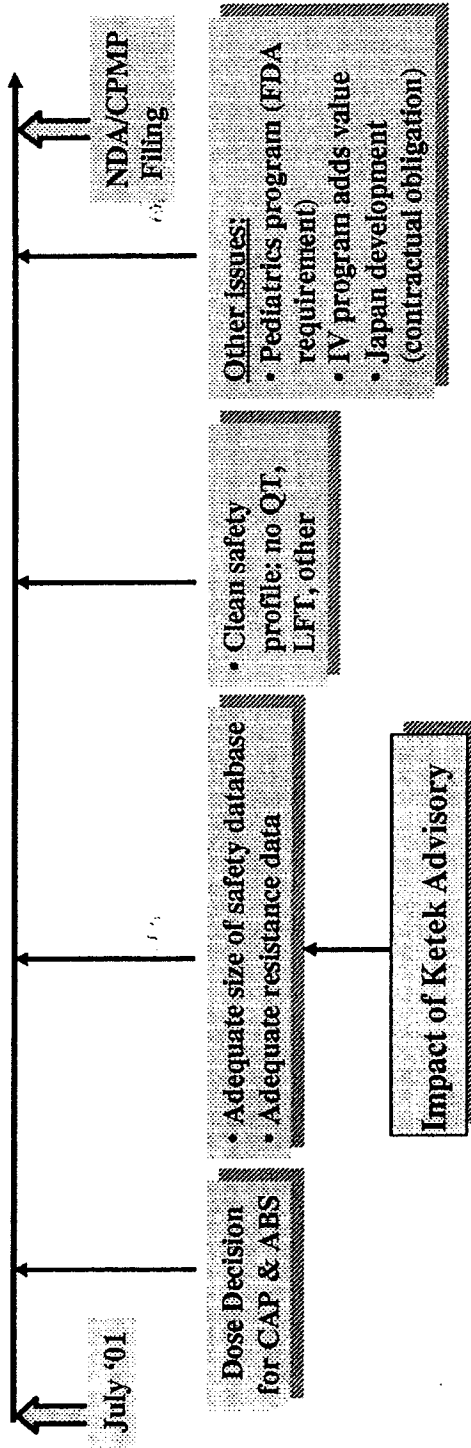
# ABT 773 Target Profile

Target Indications		
ABECB	5D	QD
ASP	5D	QD
CAP	10D	QD/BID
ABS	10D	QD/BID

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS QD/BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates	Under exploration	Claim for pen-R Strep pneumo (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver	Approved	Approved	Approved	Large database condition for approval US, EU approval <sup>3</sup>



Filing date dependant on timing of Dose decision and  
Program size.  
Program dependant on technical and regulatory  
hurdles



	Impact	Cost	Timing
Resistance	size of database	\$54MM	12 mo delay
Safety	concern over QT, liver issues	\$4.0MM	No impact

# Impact of Ketek FDA Advisory

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS QD/BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates <b>Increased to 25 isolates</b>	Under exploration	Claim for pen-R <i>Strep pneumo</i> (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver <b>Added 1000 patients</b>	Approved	Approved	Approved	Large database condition for approval US, EU approval

## Impact of Dose Decision

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates <b>Increased to 25 isolates</b>	Under exploration	Claim for pen-R <i>Strep pneumo</i> (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver <b>Added 1000 patients</b>	Approved	Approved	Approved	Large database condition for approval US, EU approval

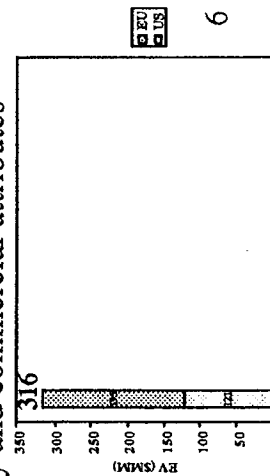
• Assessed six alternative strategies based on technical, regulatory and commercial attributes

• Chose BID dose pending results of ABS and CAP studies

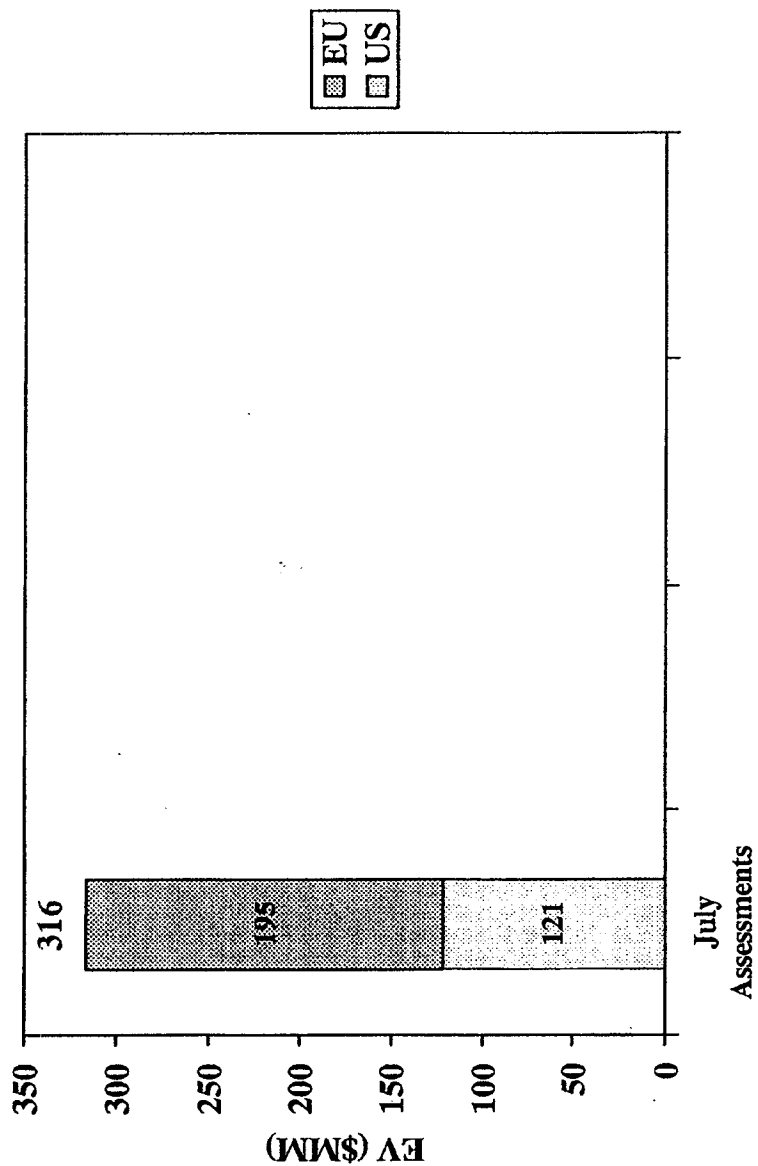
• Start pivotal studies in 2001 winter season

• PK/PD parameters

• Statistical probability of success in comparator studies



ABT 773 Expected Value  
based on Ketek and Dose decision



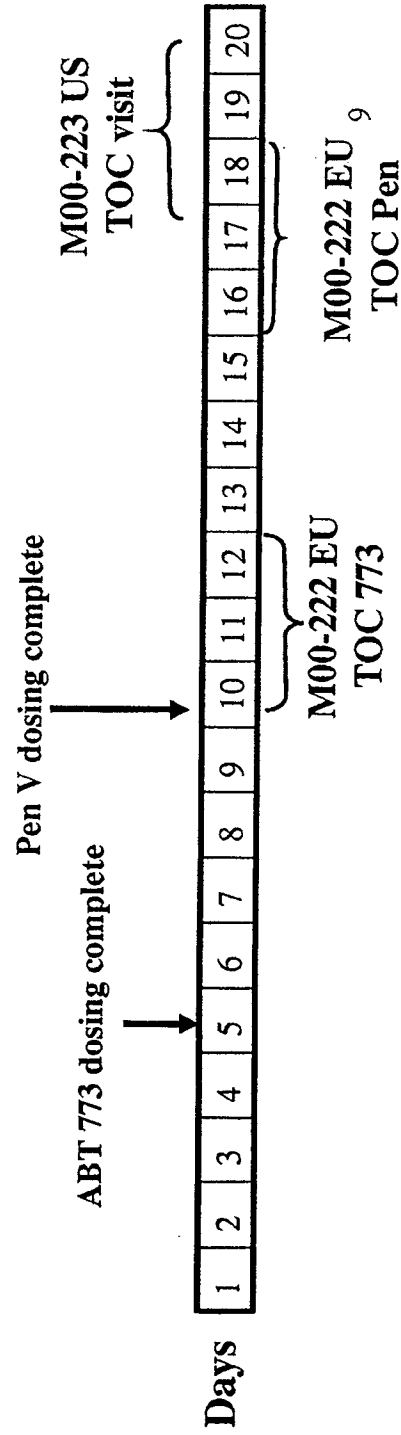
# ABT-773 Phase III Clinical Plan (Pivotal Trials)

Study	Indication	Comparator	Number ABT-773 Subjects	ABT-773 Dose/ Duration in Days	Status
US, EU (IND) M00-225	Sinusitis	NA	660	150 BID x 10 d 150 QD x 10 d	84-86% interim analysis
US, Canada (IND)	Sinusitis	Augmentin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	Sinusitis	Quinolone	660	150 BID x 10 d	Ready to dose
US (IND) M00-219	CAP	NA	600-800	150 BID x 10 d 150 QD x 10 d	585/600 Unblind Jan
US (IND)	CAP	Levofloxacin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	CAP	Amoxicillin	660	150 BID x 10 d	Ready to dose
US	Pharyngitis	Penicillin	520	150 QD x 5 d	Failed
EU	Pharyngitis	Penicillin	520	150 QD x 5 d	209/520
US	ABECB	Azithromycin	600	150 QD x 5 d	578/600
EU	ABECB	Levofloxacin	500	150 QD x 5 d	327/500

## US: M00-223 (IND study)

### ABT-773 150 mg QD VS Penicillin V 500 mg TID Streptococcal Pharyngitis/Tonsillitis

- Treatment groups :
  - ABT-773 150 mg on Study Days 1-5
  - Penicillin V 500 mg (250 mg x 2) TID tablets on Study Days 1-10
- 2 different protocol designs for Test-of-Cure (TOC) Visits EU vs US



**M00-223 US Pharyngitis Study**  
**Eradication Rate at Test-of-Cure Visit**

	<b>ABT-773</b>	<b>Penicillin</b>	<b>95% CI</b>	<b>P-value</b>
<u><b>Bacteriological</b></u>				
<b>PP</b>	74% (140/189)	90% (170/189)	(-23.7, -8.0)	<0.001
<b>ITT</b>	64% (141/220)	81% (171/212)	(-25.1, -8.0)	<0.001
<u><b>Clinical</b></u>				
<b>PP</b>	85% (160/188)	93% (175/188)		

# Pharyngitis and earlier Sinusitis

## Data are Consistent

- Pharyngitis indication: test of cure is bacteriological  
Sinusitis cure rates 86% BID vs 84% QD based on clinical cure with presumed eradication.
- Indications at different doses;
  - Sinusitis 150 mg QD less effective than 150 mg BID even at 10 days
  - Pharyngitis result findings consistent with clari failure at 5 days and success at 10 days therapy
- Sinusitis had no comparator and will still be tested



## Impact of Pharyngitis Results on Bronchitis Indication at 150mg QD

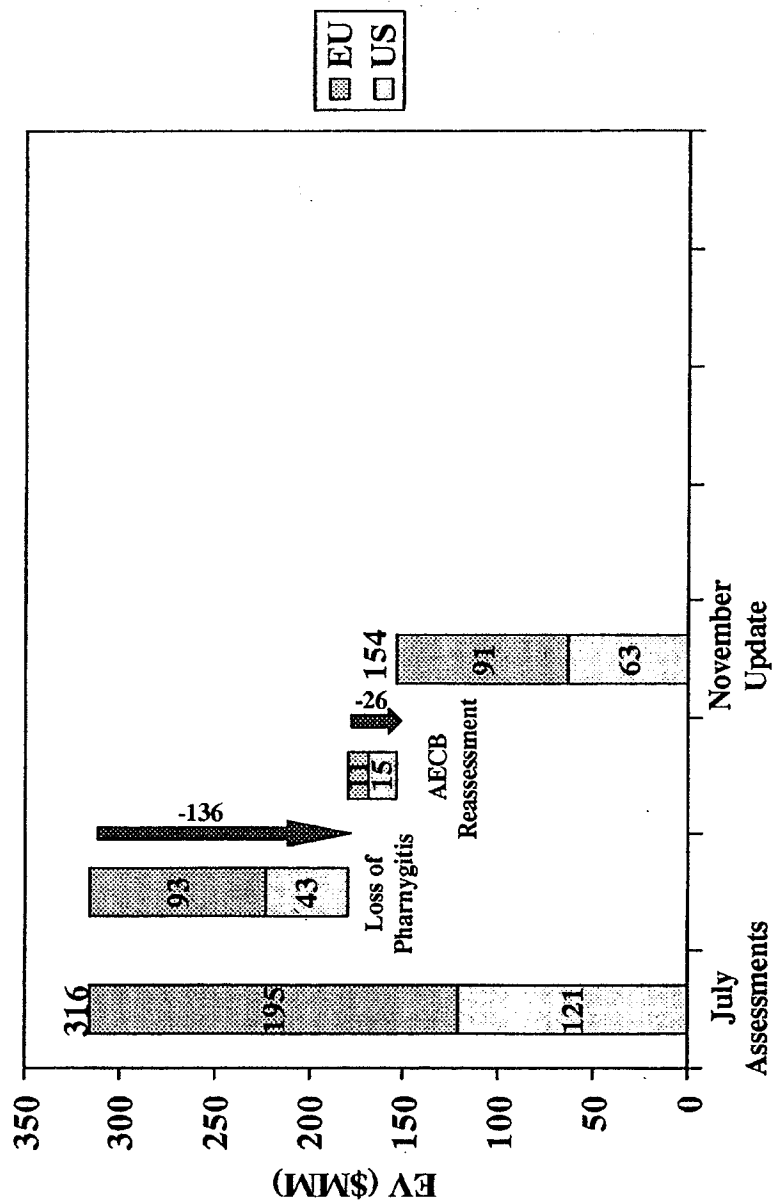
- Bronchitis trial likely to succeed based on clinical cure rate (blinded clinical rate 82%)
  - Placebo effect
  - Enriched population FEV1 and FEV1/FVC
- Bacteriological failure in pharyngitis raises issues of bacteriological efficacy at 150mg QD dose
  - *S. pyogenes* and *S. pneumoniae* have similar MIC profiles
  - *H. influenzae* in bronchitis is an important pathogen
- Bronchitis is only indication left at 150mg QD dose
  - will not be supported by CAP data (occult CAP a clinical concern)
- EU approach to bronchitis

## Impact of Dose Decision

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS BID	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates <b>Increased to 25 isolates</b>	Under exploration	Claim for pen-R <i>Strep pneumo</i> (15/15 isolates)	None	Not obtained, pen-R and mac-R (14/17 isolates)
Safety	QT, liver <b>Added 1000 patients</b>	Approved	Approved	Approved	Large database condition for approval US, EU approval

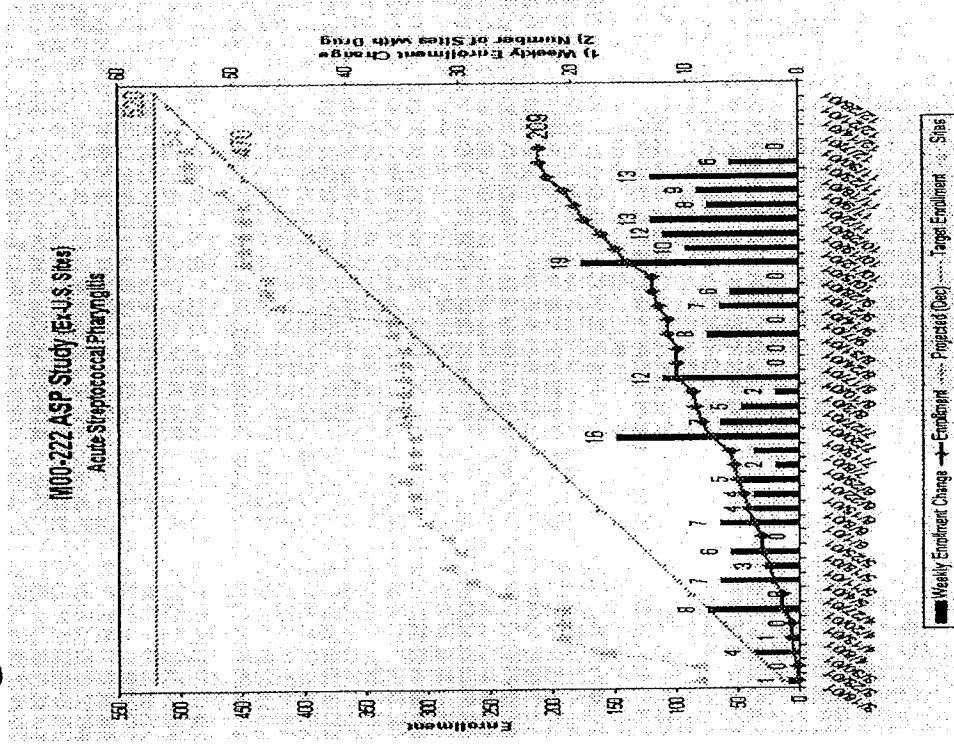
- Possibility of a QD follow on is limited
- ASP repeat studies thought to be commercially non-viable

# ABT 773 Expected Value based on ABS/ASP results




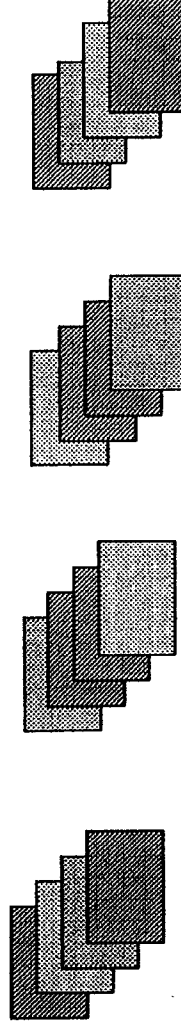
## Recommend Closing EU ASP Trial

- Indication with 150mg QD lost:
  - US: Non-approvable, less than 85% bacteriological cure and less than 10% difference
  - EU: Likely non-approvable, less than 10% difference to Penicillin and >80% in 2 trials
- Issue is the communication



## M01-325 QT Study Design

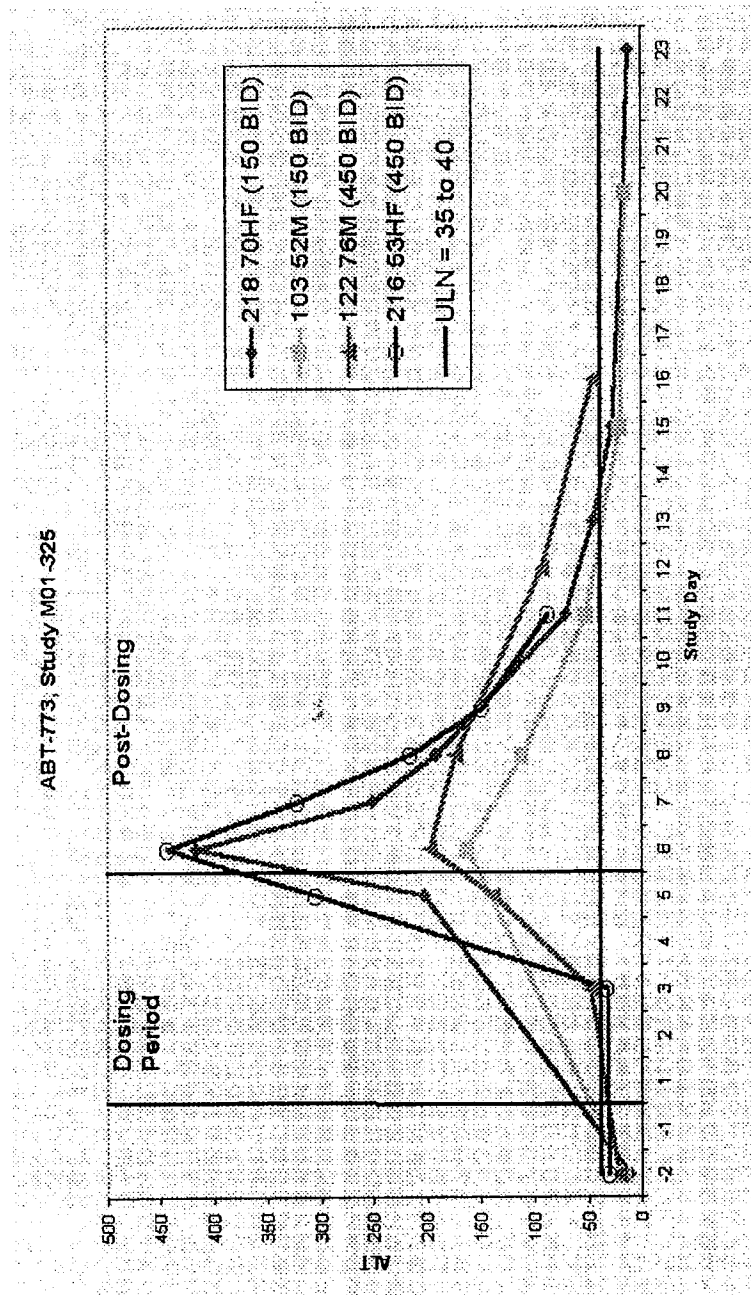
- 68 Healthy males and females, 20% greater than 50 years old.
- Double-blind, multiple-dose, four-period crossover each period dosing 5 days, 10 day washout
-  Placebo, 150 mg BID, 300 mg BID, 450 mg BID
- Randomized, into 1 of 4 sequences containing



Each period ECG collection:

Day -1 Placebo baseline, Day 1, Day 5 ECG and PK

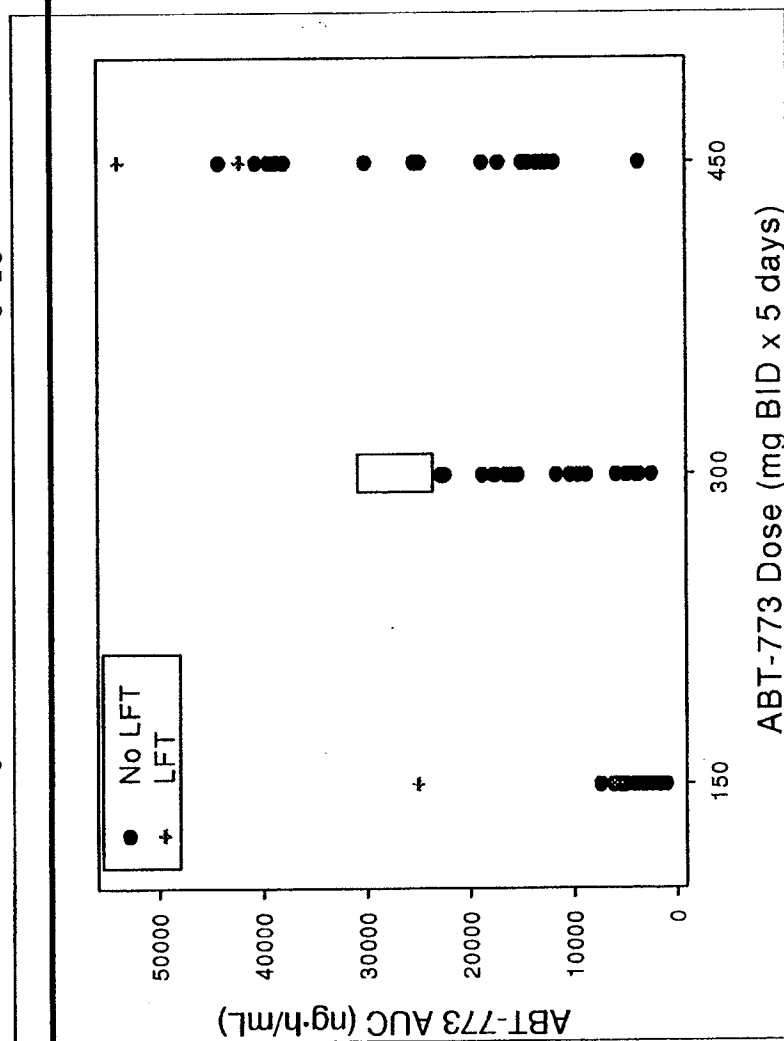
# Study M01-325: 4 Subjects with Significantly Elevated ( $>3 \times \text{ULN}$ ) ALT (All $>50$ years old)



2 subjects at 150mg BID and 2 subjects at 450mg BID

ABBT271800

# Study M01-325: Relationship Between Dose and Day 5 ABT-773 AUC<sub>0-18</sub>

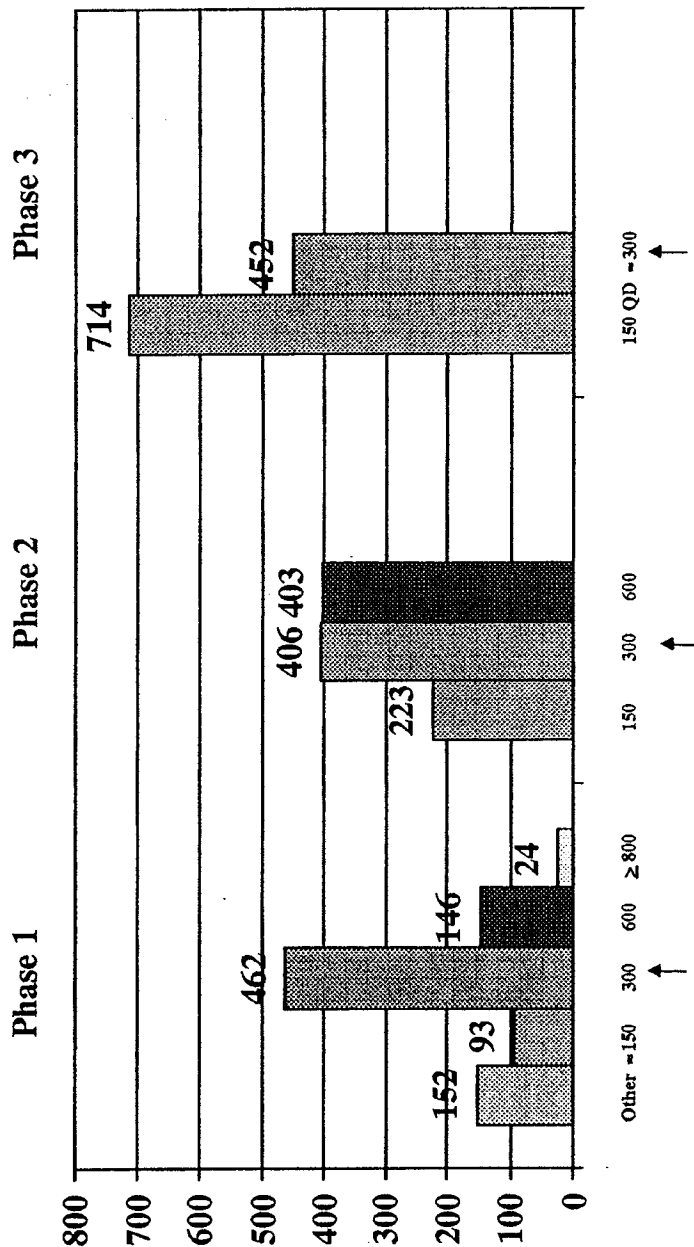


18

LFT = Subjects 103, 122, 216 and 218; No LFT = All other subjects.

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# No. of Subjects Available for Analysis



Other: single dose or blind data



# Overall Incidence of LFT's Not Changed (All Subjects with LFT)

	$\geq 3 \times \text{ULN}$
Original overall N=2884	39 (1.4%) [1.0, 1.8]
New overall N=2939	43 (1.5%) [1.1, 2.0]
Current Phase 3 N=1047	17 (1.6%) [0.9, 2.6]

**Investigation of the Available Database Exhibits No  
Concern for Continuing at 150mg BID and 300mg BID  
Overall ALT Abnormality Rates in Phase 2 and 3  
(Normal at Baseline -- ALT <1x ULN)**

	> 1x ULN	≥ 2x ULN	≥ 3x ULN	≥ 5x ULN
<b>150 mg QD</b>	71/738 (9.6%) [7.6, 12.0]	8/738 (1.1%) [0.5, 2.1]	3/738 (0.4%) [0.1, 1.2]	2/738 (0.3%) [0, 1.0]
<b>150 mg BID alone</b>	38/344 (11.0%) [7.9, 14.8]	4/344 (1.2%) [0.3, 3]	1/344 (0.3%) [0, 1.6]	0 (0, 0.8]
<b>300 mg daily (includes 150 mg BID)</b>	88/667 (13.2%) [10.7, 16.0]	8/667 (1.2%) [0.5, 2.3]	3/667 (0.4%) [0.1, 1.3]	0 (0, 0.6]
<b>600 mg daily</b>	59/327 (18.0%) [14.0, 22.6]	8/327 (2.4%) [1.1, 4.8]	2/327 (0.6%) [0.1, 2.2]	1/327 (0.3%) [0, 1.7]

- Only 24 patients at doses 800mg or above
- Dose response demonstrated increases at 600 mg

## ALT Changes at Post-Therapy 1-2 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Clari ER* N=783	ABT-773& 150 mg QD N=574	ABT-773@ 150 mg BID N=328	ABT-773 # 300 mg N=633	ABT-773 ^ 600 mg N=314
>1x ULN	35 (4.5)	50 (8.7)	24 (7.3)	55 (8.7)	39 (12.4)
≥ 2x ULN	3 (0.4)	6 (1.0)	3 (0.9)	6 (1.0)	2 (0.6)
≥ 3x ULN	0	2 (0.3)	1 (0.3)	2 (0.3)	0
≥ 5x ULN	0	1 (0.2)	0	0	0

\*Clari ER Phase 3, ABECB, ABS and CAP.

&Phase 2 and 3; @Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

^ Phase 2, including 200mg TID and 600mg QD.

¶ Number (%)

## ALT Changes at Post-Therapy 7-14 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Ketek N=1232*	Comparator N=1031*	ABT-773 <sup>&amp;</sup> 150 mg QD N=618	ABT-773 <sup>@</sup> 150 mg BID N=302	ABT-773 <sup>#</sup> 300 mg N=598	ABT-773 <sup>^</sup> 600 mg N=273
>1x ULN <sup>†</sup>	98 (8.0)	92 (8.9)	36 (5.8)	23 (7.6)	46 (7.7)	34 (12.5)
≥2x ULN	6 (0.5)	4 (0.4)	2 (0.3)	1 (0.3)	3 (0.5)	4 (1.5)
≥3x ULN	1 (0.1)	3 (0.3)	1 (0.2)	0	1 (0.2)	2 (0.7)
≥5x ULN	0	0	1 (0.2)	0	0	1 (0.4)

\*Ketek Phase 3  
<sup>&</sup>Phase 2 and 3; <sup>@</sup>Phase 3; <sup>#</sup>Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.  
<sup>^</sup>Phase 2, including 200mg TID and 600mg QD.  
<sup>†</sup>Number (%)

# Maximum ALT Changes in Phase 3 CAP (Ketek, Clari ER, ABT-773)

## Studies in Subjects with Normal Baseline Values

ALT Value	Ketek 800 mg QD N=395	Clari ER 1000 mg QD N=121	ABT-773 150 mg BID N=148
>1x	86 (21.8)	14 (11.6)	17 (11.5)
≥2x	14 (3.5)	5 (4.1)	2 (1.4)
≥3x	4 (1.1)	0	1 (0.7)
≥5x	1 (0.3)	0	0

## No “Index” Case to Date in ABT-773

- Up to 3% 3x ULN LFTs acceptable in antibiotics  
(CDER-PhRMA-AASLD conference Nov 2000)
- Asymptomatic
- Reversible
- No change in bilirubin (Hy’s law)
- No chronicity

Ketek had 2 index cases

This can drive an increased database need.

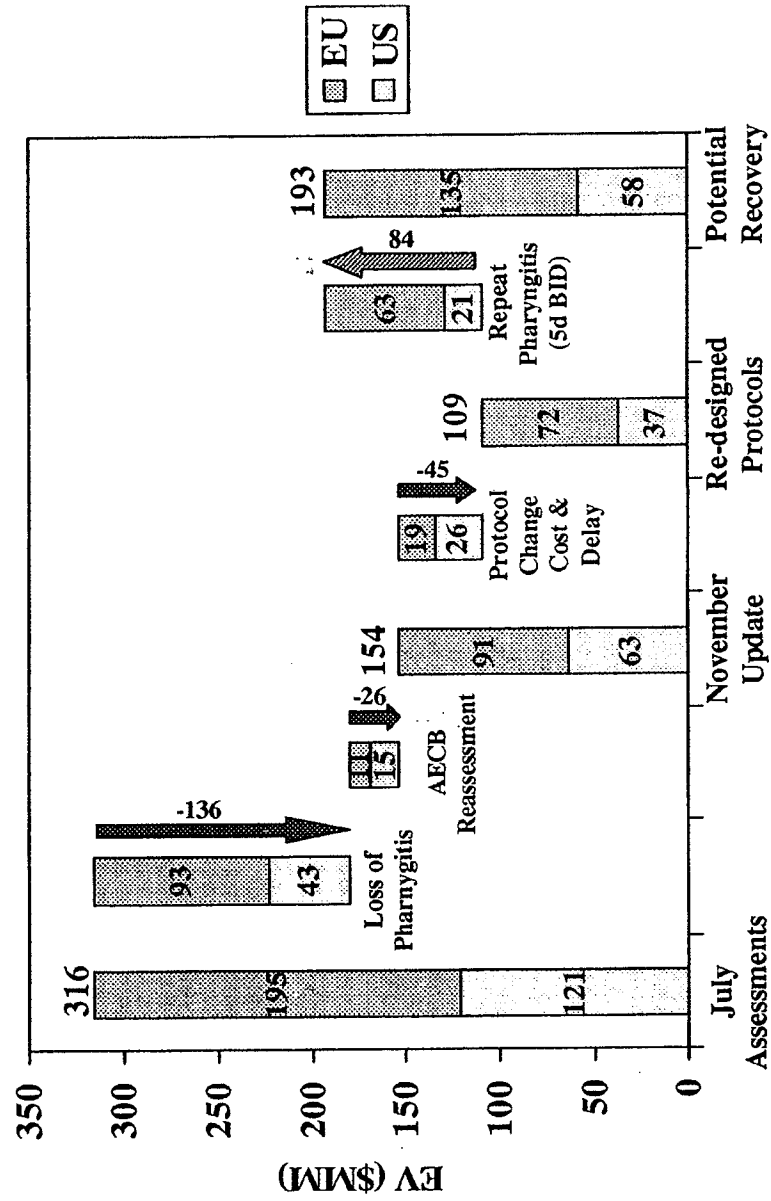
Quinalones—5000 patients

“Hy’s law”—10 000 patients

## Conclusions from Complete Analysis of LFTs

- Overall average event rate is relatively unchanged
  - 4 cases in QT study
  - (7 cases in Japanese bridging study)
- Definite drug effect with possible dose effect (Possible AUC relation)
- No. of patients with  $\geq 3$ x ULN ALT well within regulatory acceptable limits for antibiotics at 150mg BID (includes phase 3 trials)
  - (CDER-PhRMA-AASLD conference Nov 2000)
- No 'index' case to date
- No single clinical identifier of patients at risk
- Recommendations to FDA
  - QT trial to recommence if practicalities allow and data still acceptable
    - Open label without 450mg BID dose
  - Protocol amendments to add Day 6 LFT and changes to informed consent recommended

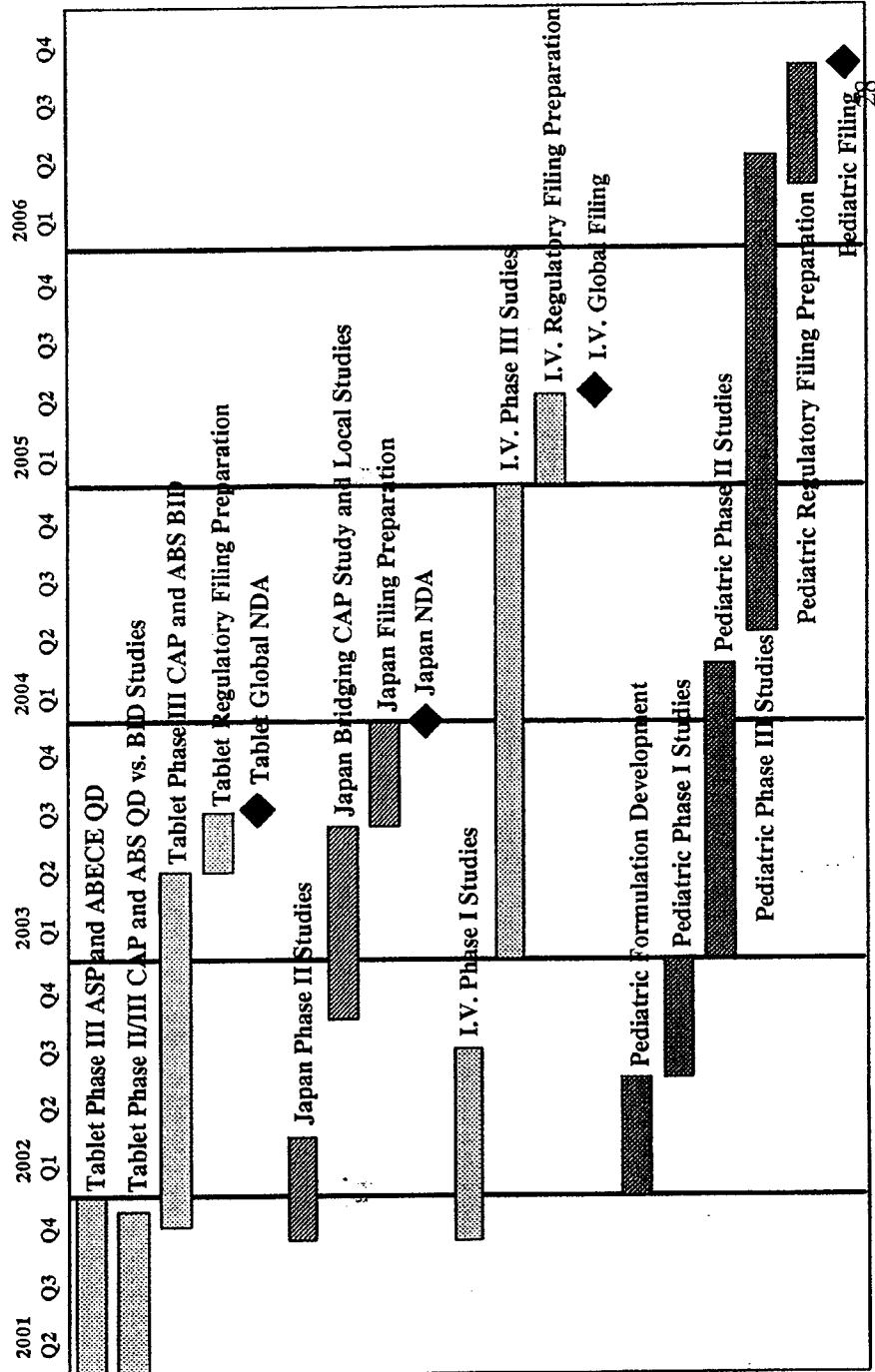
# Current ABT 773 Expected Value Assessment



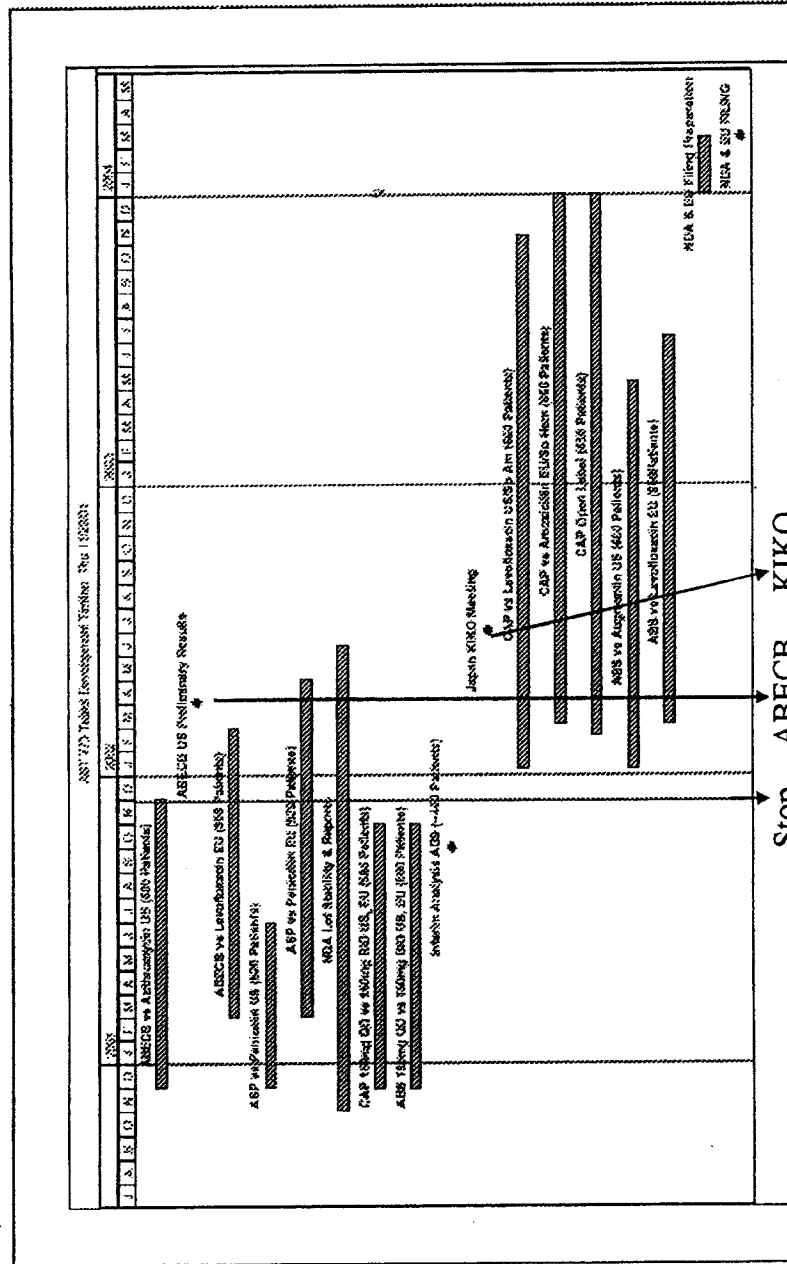
Additional LFT regulatory risk has not been quantified in the above analysis.<sup>27</sup>



# ABT-773 Development Program – Tablet, Japan, I.V. and Pediatric Plans



# ABT 773 Current Development Plan



2002 Budget  
\$79.3MM

Today	Outcome	Outcome
-------	---------	---------

Today	Outcome	Outcome
-------	---------	---------

29.0 54.5 67.5

Exit Costs (\$MM)

ABBT271812

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- Back up

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Regulatory experience defined new regulatory standards which determines program size:

- Size of the safety database is driven by the product **benefit/risk** profile:
  - Ketek's 3200 patient safety database insufficient, ?liver/QT.
- A resistance claim will significantly support benefit risk:

Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	1563	781
30	2182	1875	938

- Importance of CAP emphasized

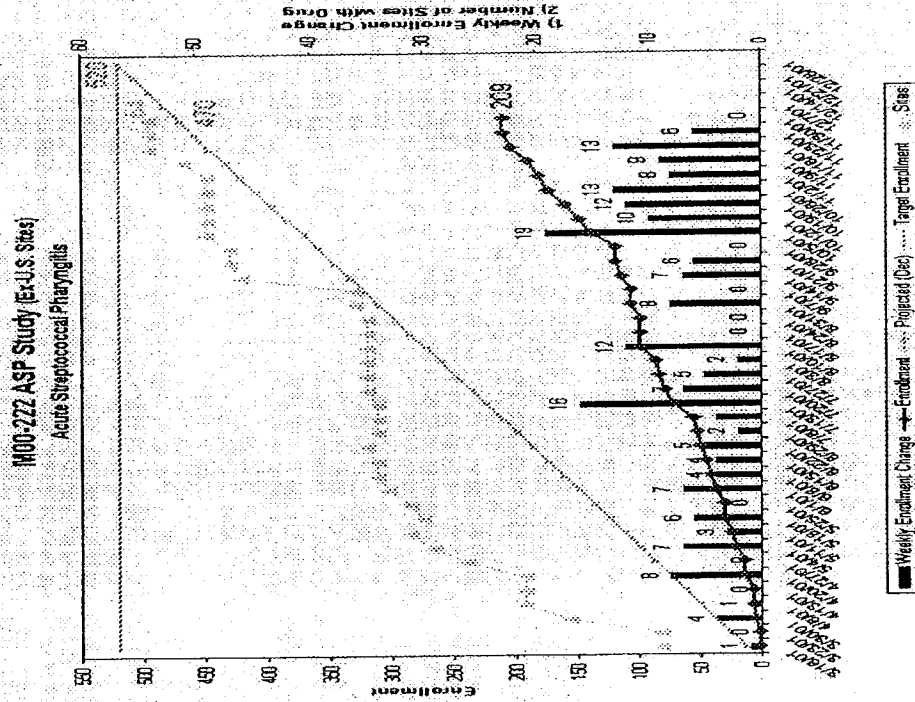
Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

1. Complete current ABS & CAP dose-ranging trials and then make dose decision. (Use ABS & CAP dose-ranging data)
2. Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. (Use ABS dose-ranging data only)
3. Select the BID dose today for ABS & CAP Ph III pivotal. (Select BID today)
4. Select the QD dose today for ABS & CAP Ph III pivotal. (Select QD Today)
5. Develop BID in CAP & ABS for EU; Develop QD for US. (QD in the US & BID in the EU)
6. Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator. (Phase III 3-arm CAP & ABS pivotal). Variation: drop arm on result availability

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## Recommend Closing EU ASP Trial

- Indication with 150mg QD lost:
  - US: Non-approvable, less than 85% bacteriological cure and less than 10% difference
  - EU: Likely non-approvable, less than 10% difference to Penicillin and >80% in 2 trials
- Issue is the communication



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ABBT271815

## ABT 773 QT issues

- Re-read key Phase I and Phase II ECG data (6749 ECGs)-completed
- Phase III studies ECGs: Ongoing studies (9085 expected)-45% completed  
Planned studies (8000 expected)
- Dedicated Phase I QT evaluation study as agreed by FDA started Sept 01 (>9000 ECGs)
  - Four-period, double-blind, placebo-control crossover designTime-matched ECGs/PK samples at day-1, day1 and steady state on day 5

**TOTAL OF 34000 ECG's: Most with correlating plasma levels of ABT773**





## ABT-773 Decision Analysis Core Team

### Anti-infective Venture

Stan Bukofzer  
Vijay Yeldandi  
Joaquin Valdes  
Carol Meyer  
Eugene Sun

### AI Regulatory Affairs

Jennifer Moore  
Nigel Livesey

### Clinical Statistics

David Morris  
Jie Zhang

### GPRD New Product Development

Rod Mittag

### Decision Support Group

Tim van Biesen  
Steve Keummerle

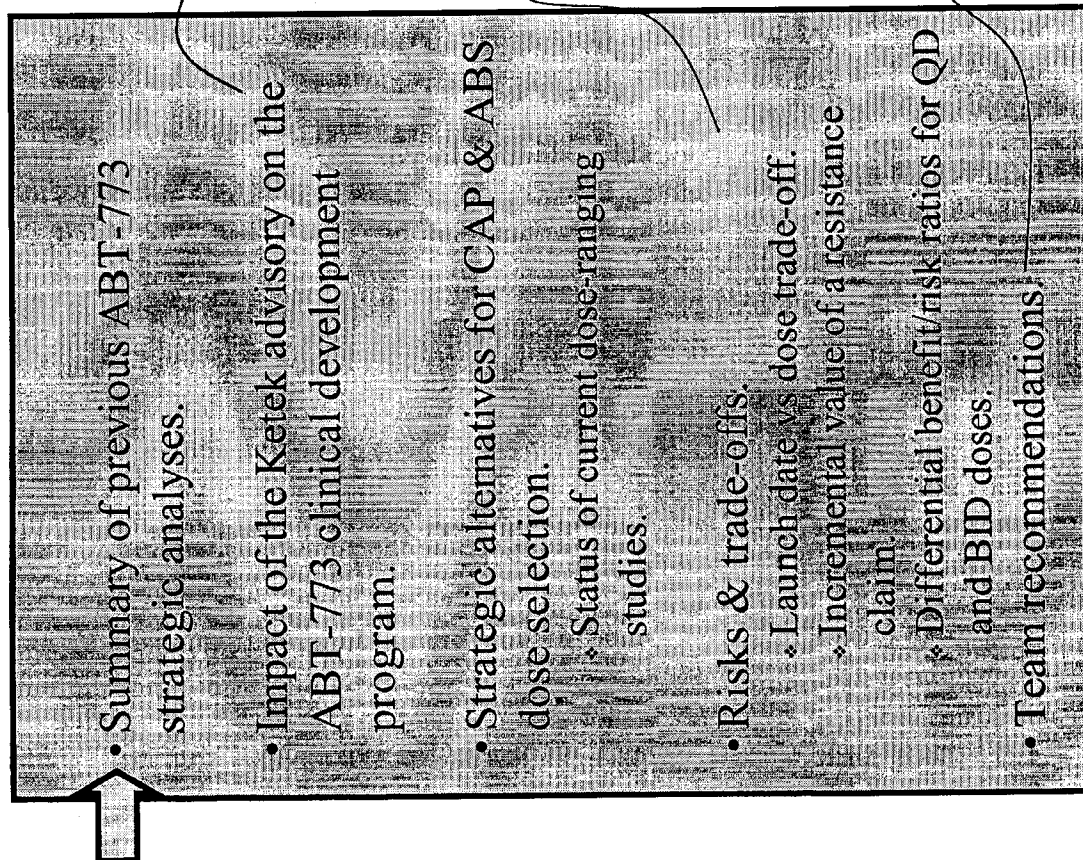
### PPD Regulatory Affairs

Jeanne Fox  
Greg Bosco

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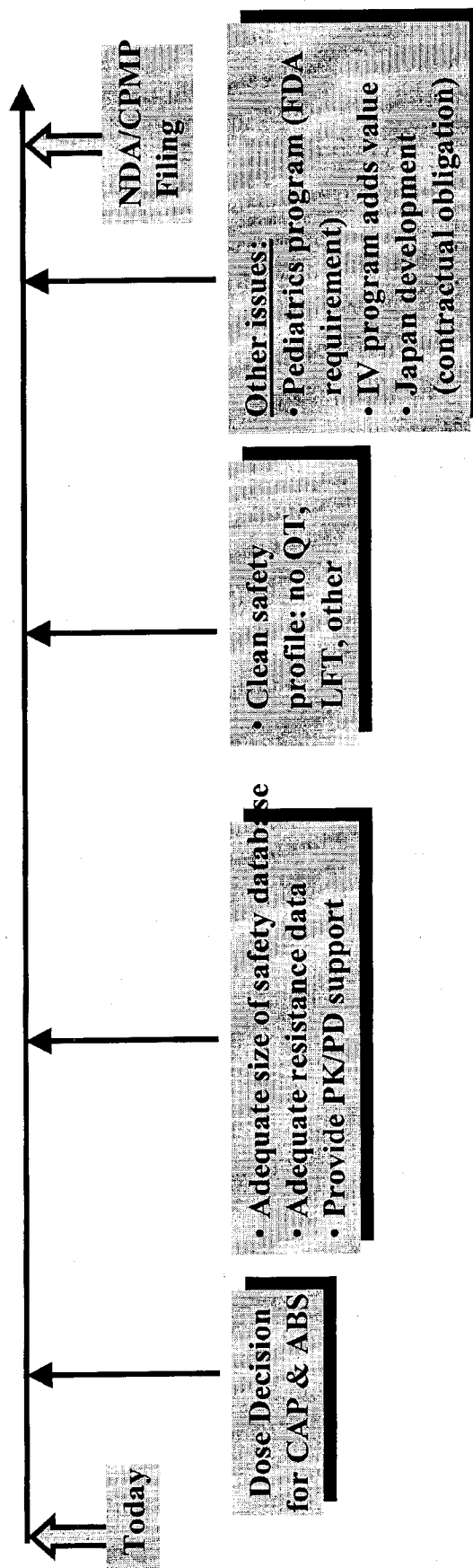
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# Meeting Agenda





Filing date dependant on timing of dose decision and  
Program size.  
Program dependant on technical and regulatory hurdles



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Ketek advisory defined new regulatory standards influences program size:

- Size of the safety database is driven by the product **benefit/risk** profile:
  - Adequacy of Ketek's 3200 patient safety database questioned, ?liver/QT.
- A **resistance claim** will significantly support benefit risk:

Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	1563	781
30	2182	1875	938

- **Importance of CAP emphasized with Sinusitis in supportive role**

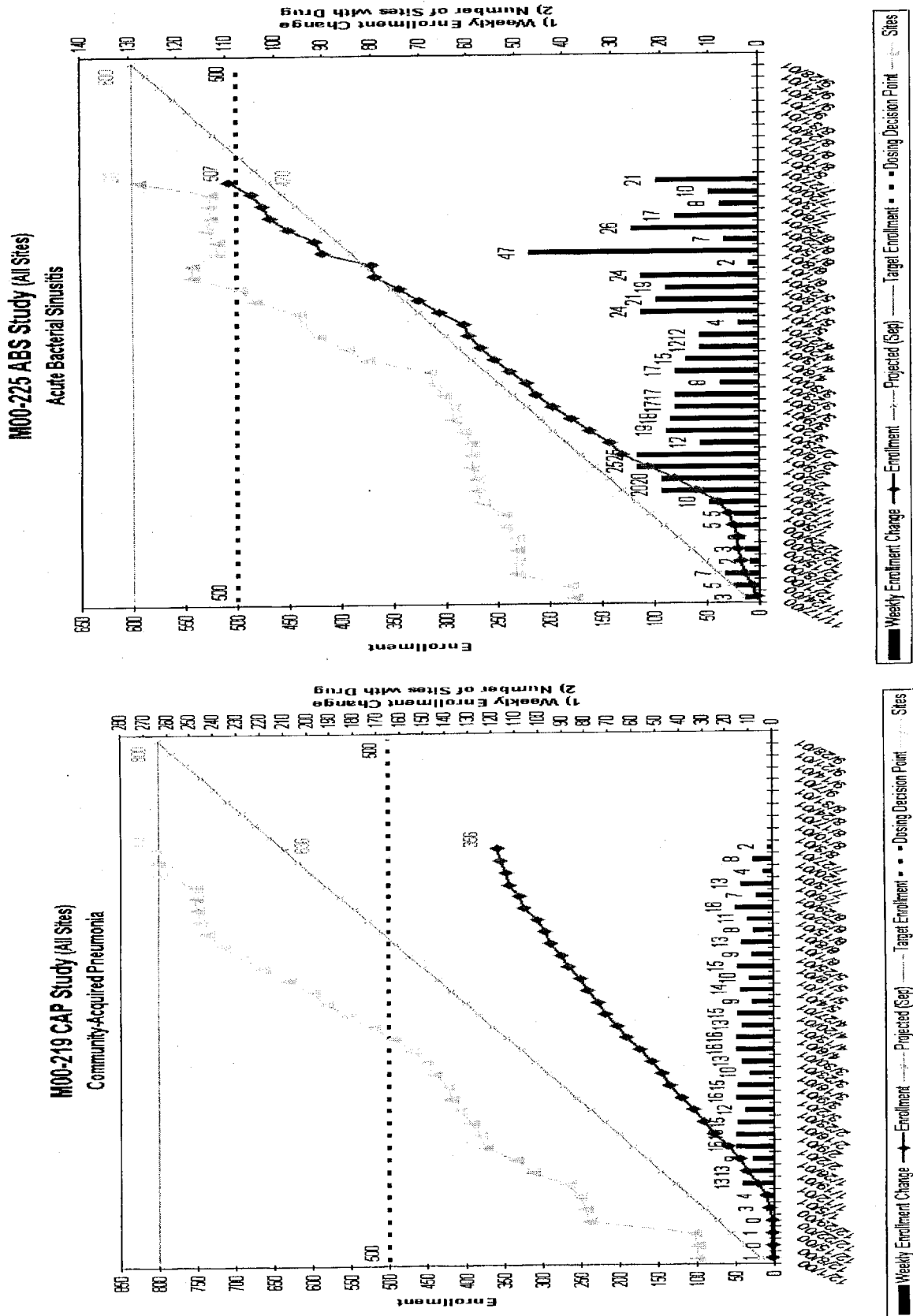
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## Current Clinical program

- AECB
  - Pivotal Studies at 150mg QD ongoing
- Pharyngitis
  - Pivotal Studies at 150mg QD ongoing
- CAP and Sinusitis
  - 150mg QD vs 150 mg BID

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Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

Strategic Alternative	Description
Use ABS & CAP dose-ranging data	<ul style="list-style-type: none"> <li>• Complete current ABS &amp; CAP dose-ranging trials and then make dose decision.</li> <li>• Complete Phase III pivotal with selected dose. <ul style="list-style-type: none"> <li>–Allows potential for split dosing for ABS &amp; CAP in the US.</li> </ul> </li> </ul>
Use ABS dose-ranging data only	<ul style="list-style-type: none"> <li>• Complete only the ABS dose-ranging study and then make a dose decision for both ABS &amp; CAP. <ul style="list-style-type: none"> <li>–If QD dose selected, obtain regulatory approval for conducting QD CAP pivotal.</li> <li>–If BID dose selected, proceed with BID dose for both ABS &amp; CAP.</li> </ul> </li> </ul>
Select BID today	<ul style="list-style-type: none"> <li>• Select the BID dose today for ABS &amp; CAP Ph III pivotal.</li> <li>• Do not wait for completion of the dose-ranging studies.</li> <li>• Pursue a post-approval QD line-extension for the US &amp; EU.</li> </ul>
Select QD Today	<ul style="list-style-type: none"> <li>• Select the QD dose today for ABS &amp; CAP Ph III pivotal.</li> <li>• Do not wait for completion of the dose-ranging studies.</li> </ul>
QD in the US & BID in the EU	<ul style="list-style-type: none"> <li>• Develop BID in CAP &amp; ABS for EU; Develop QD for US.</li> <li>• Do not wait for completion of the dose-ranging studies.</li> </ul>
Phase III 3-arm CAP & ABS pivots	<ul style="list-style-type: none"> <li>• Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator.</li> <li>• Drop one arm and continue with selected dose only (vs comparator).</li> </ul>

Four alternatives were shown to be not feasible due to regulatory and technical constraints (I).

- **“Select QD Today” and “QD in the US & BID in EU”:**
  - Both of these alternatives require that Phase III pivots are initiated with the QD dose prior to the completion of the dose-ranging studies.
  - Given that Abbott sought out FDA approval for the current Phase III dose-ranging studies, there is a <10% probability that we would be permitted to proceed with the lower dose without supporting data.
  - In EU skepticism expressed at AQD dose; could impact approvals of Phase III
- **“Phase III 3-arm CAP & ABS pivots” variations thereof (ie, drop arm)**
  - Without dropping an arm:
    - Increases numbers by 1/3
    - Defers decision to end of Phase 3
    - Risk due to 2<sup>nd</sup> study, giving different outcome for doses

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Four alternatives were shown to be not feasible due to regulatory and technical constraints (II).

- **Phase III 3-arm CAP & ABS pivots**” variations thereof (ie, drop arm)
  - Dropping arm when CAP data available
    - There is no precedent for the FDA allowing the dropping of an arm during Phase III in a pivotal. FDA might not sanction trial to start given dose trials ongoing.
    - Dropping arm will require scientific amendment, could potentially be refused by some authorities (EU)
    - Statistical challenges of randomizing block size, but not limiting
- **Deferring dose decision to sinusitis data**
  - does not allow sufficient assurance for extrapolating to CAP, unless if BID dose preferred choice..discussed later
  - significant regulatory issues with splitting dose between CAP and sinusitis
  - early blind break , while statistically feasible has significant regulatory risk.

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The estimated NDA filing date and launch is impacted by the timing of the QD/BID dose decision.

Dose Selection Strategy	Dose Decision Date	Phase III		NDA Filing	Expected launch
		Start	Finish		
Select BID Today	Jul 01	Nov 01	Jun 03	Oct 03	Winter 04
Use ABS & CAP dose-ranging data	Mar 02	Sep 02	Dec 03	Apr 04	Winter 05

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## Key technical assumptions.

- Probability that ABT-773 achieves a resistance claim, given sufficient enrollment:
  - QD dose: 60%
  - BID dose: 80%
- Current dose-ranging studies:
  - Probability that ABS QD dose is <10% different from BID: 50%
  - Probability that CAP QD dose is <10% different from BID: 75%
- Phase III risk assessments:
  - Probability QD dose succeeds in ABS: 25%
    - This probability increases to 35% if dose-ranging shows statistical non-inferiority.
  - Probability BID dose succeeds in ABS: 65%
  - Probability QD dose succeeds in CAP: 65%
    - This probability increases to 75% if dose-ranging shows statistical non-inferiority.
  - Probability BID dose succeeds in CAP: 85%

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## Key commercial assumptions.

- Base Peak Sales Forecast:
  - US: \$432MM
  - EU: \$295MM
- Impact of BID dosing:
  - US: 23% loss of share vs QD (up to 50%)
  - EU: 21% loss of share vs QD
- Impact of Ph IV QD line extension if BID dose is selected today:
  - US: 20% recovery of lost share
  - EU: 50% recovery of lost share
- Impact of launching with a resistance claim:
  - US: 32% increase in share
  - EU: 49% increase in share

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## Key regulatory assumptions.

- CAP is critically important to product approval in both the EU and US.
- EU regulatory risk is high if either ABS or CAP fail to meet clinical endpoints.
- ABT-773 PK/PD data are most important for EU approval. FDA more likely to be convinced by clinical cure rates.
- A resistance claim significantly increases the probability of regulatory approval in both the US & EU.
- Given that FDA input was solicited for the current dose-ranging study, there is a very small probability that we would be permitted to proceed with a QD dose without supporting data (i.e. before ABS & CAP dose-ranging data are available).
- Selection of the 150 mg BID dose prior to completion of the dose-ranging data is likely to be acceptable to all regulatory agencies.

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Selecting a BID dose today has a higher expected value than waiting for the dose-ranging data.

Strategic Alternative	Expected Value (\$MM)		
	US	EU	WW
Select BID Today	137	202	339
Wait for Dose-Ranging Data	147	112	259

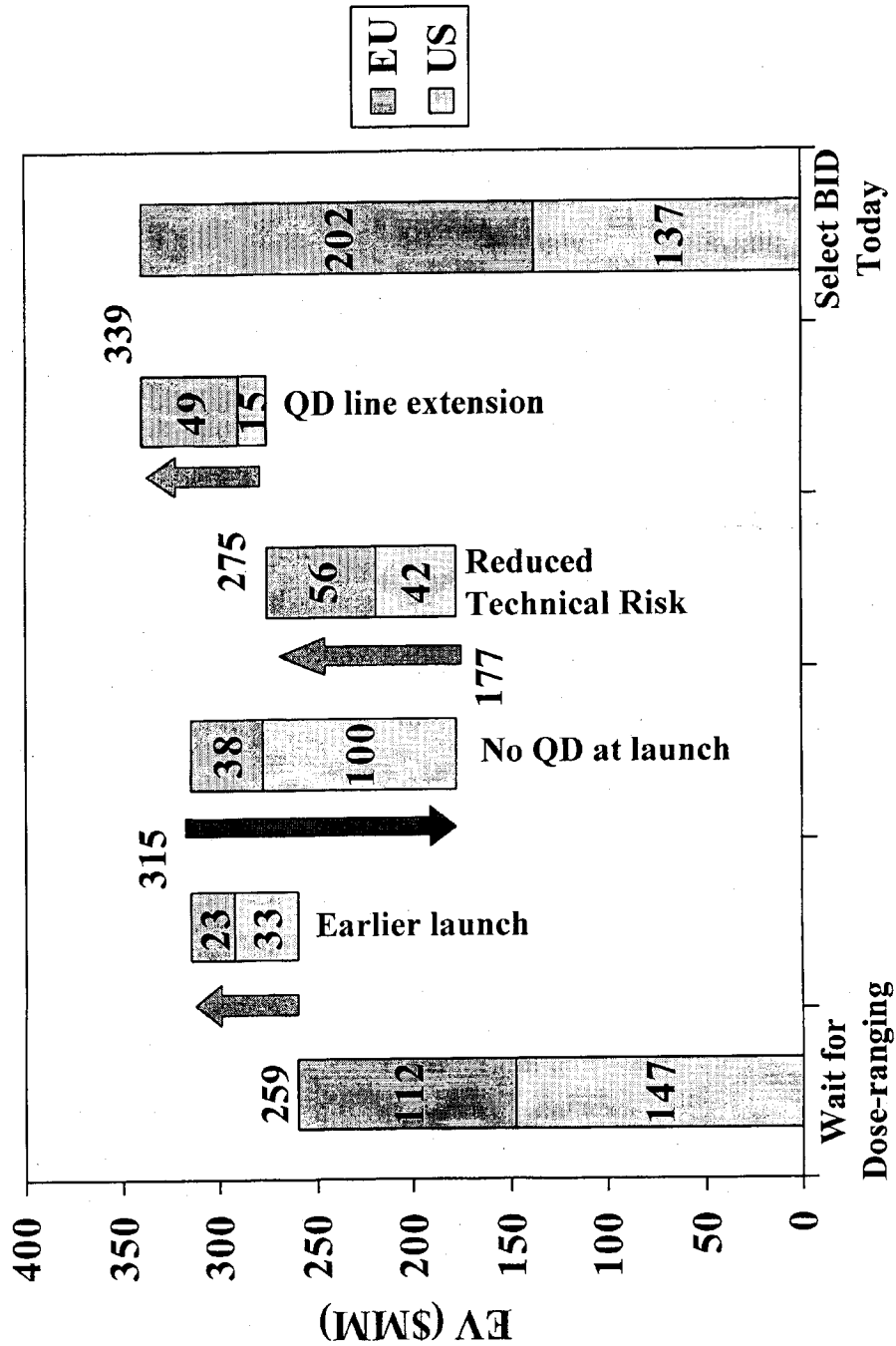
- The expected value of ABT-773 in the US is slightly increased by exploiting every opportunity for a QD dose:
  - The commercial penalty for BID dosing in the US is significant:
    - 23% loss of share if both CAP & ABS are BID.
    - 20% recovery of share with a post-launch QD line extension.
- The expected value of ABT-773 in the EU is maximized by pursuing the shortest possible path to market:
  - In the EU, the penalty for BID dosing is less severe:
    - 21% loss of share if CAP & ABS are BID.
    - However, 50% recovery of share with a post-launch QD line extension.

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# PART 2

The adverse commercial impact of selecting BID today is offset by reduced technical risk, accelerated timelines, and the option to follow with a QD line extension.



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## Sensitivity to technical inputs.

- The base model shows that the dose-ranging data does not add incremental value over selecting BID today.
  - This is due, in part, to the assumption that the QD dose in ABS has only a 35% probability of technical success in Phase III, even when it is shown to be non-inferior (<10% difference from BID) during the dose-ranging study.
  - The probability of success in Phase III must be >50% to choose to wait for the dose-ranging data.
  - The QD dose in CAP has a 75% probability of success, given that non-inferiority was shown in the dose-ranging study.
  - Due to the critical regulatory importance of CAP, this probability must exceed 95% to choose to wait for the dose-ranging data.

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## Sensitivity to commercial inputs.

- In the US, waiting for the dose-ranging data has a slightly higher expected value than selecting BID today – this is due, in part, to:
  - The adverse commercial impact of the BID dose (23% loss of share).
    - Waiting for the dose-ranging data has higher value for all assessments greater than a 22% loss of share due to BID dosing.
    - Base case assumes 23% share loss based on market research.
    - US Marketing believes share loss could be as high as 50% at which point either strategy has equivalent worldwide expected value.
  - A Ph IV QD line extension is expected to recover only 20% of the lost share.
    - Selecting BID today is warranted only if more than 30% of lost share can be recovered with a Ph IV QD line extension (within two years of launch).
    - However, the share recovery must be significantly higher if the initial impact of BID dosing is –50%.
- In the EU, selecting BID today has a higher value:
  - The impact of launching with a BID dose (21% share loss) is mitigated by the QD line extension which can recover up to 50% of lost share.
  - Initial share loss can be as high as 60% before choosing to wait for dose-ranging data.

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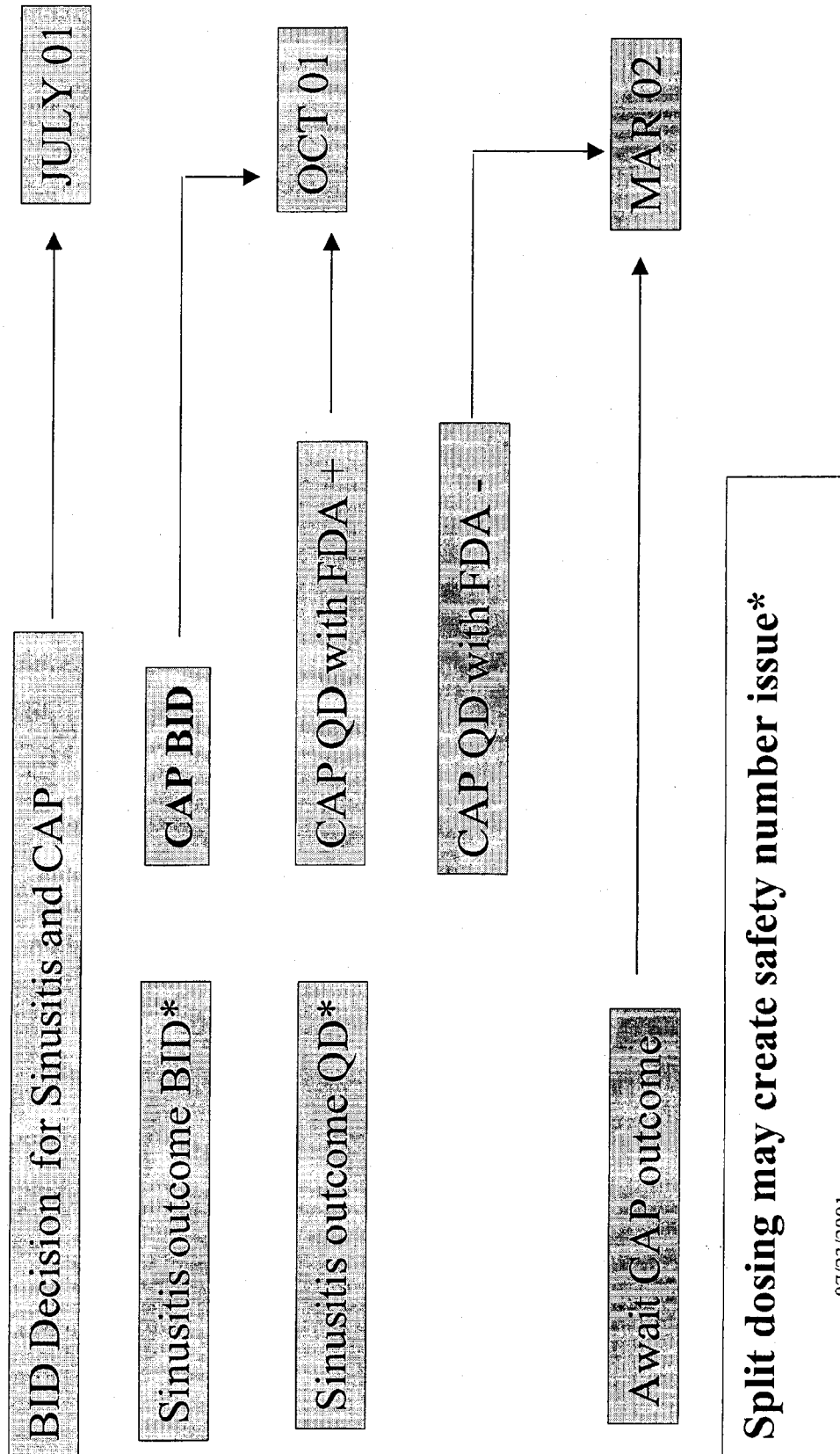
## Key conclusions.

- The expected value of selecting the BID dose today exceeds the value of waiting for the dose-ranging data.
  - The earlier launch date, reduced technical risk, and option to pursue a Ph IV QD line extension outweigh the adverse commercial impact of launching at the BID dose.
- These conclusions are robust under a broad range of technical and commercial assumptions.
  - The adverse impact of a BID dose in the US must exceed 50% before choosing to wait for the dose-ranging data.
- A favorable outcome for the QD dose in the dose-ranging study does not significantly increase the probability of technical success in Phase III.

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## Timing of Dose decision



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## Criteria for QD dose decision

### Difference between QD and BID

- Cure rate in ITT and PP population meets confidence interval criteria
- Efficacy in bacteriologically evaluable population is not statistically different between the 2 groups
- Pathogen eradication rates are not statistically different between the 2 groups
- Observed difference in clinical cure rate of QD vs BID does not exceed X %

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Preliminary PP Clinical Response  
Blinded Data

	Cure	Failure	Ind.	Total
CAP	158 (92%)	14	32	204
Sinusitis	230 (83%)	46	21	297
ABECB	309 (84%)	60	26	395
Phary.	362 (87%)	55	30	447

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# Power to Demonstrate Equivalence in a Phase 3 Trial

	Cure Rate = 90%			Cure Rate = 85%			Cure Rate = 80%		
	500	660	750*	500	660	750*	500	660	750*
0%	92%	97%	97%	80%	90%	90%	71%	82%	82%
2%	73%	84%	85%	59%	67%	72%	50%	62%	63%
4%	46%	57%	59%	36%	42%	47%	31%	38%	39%

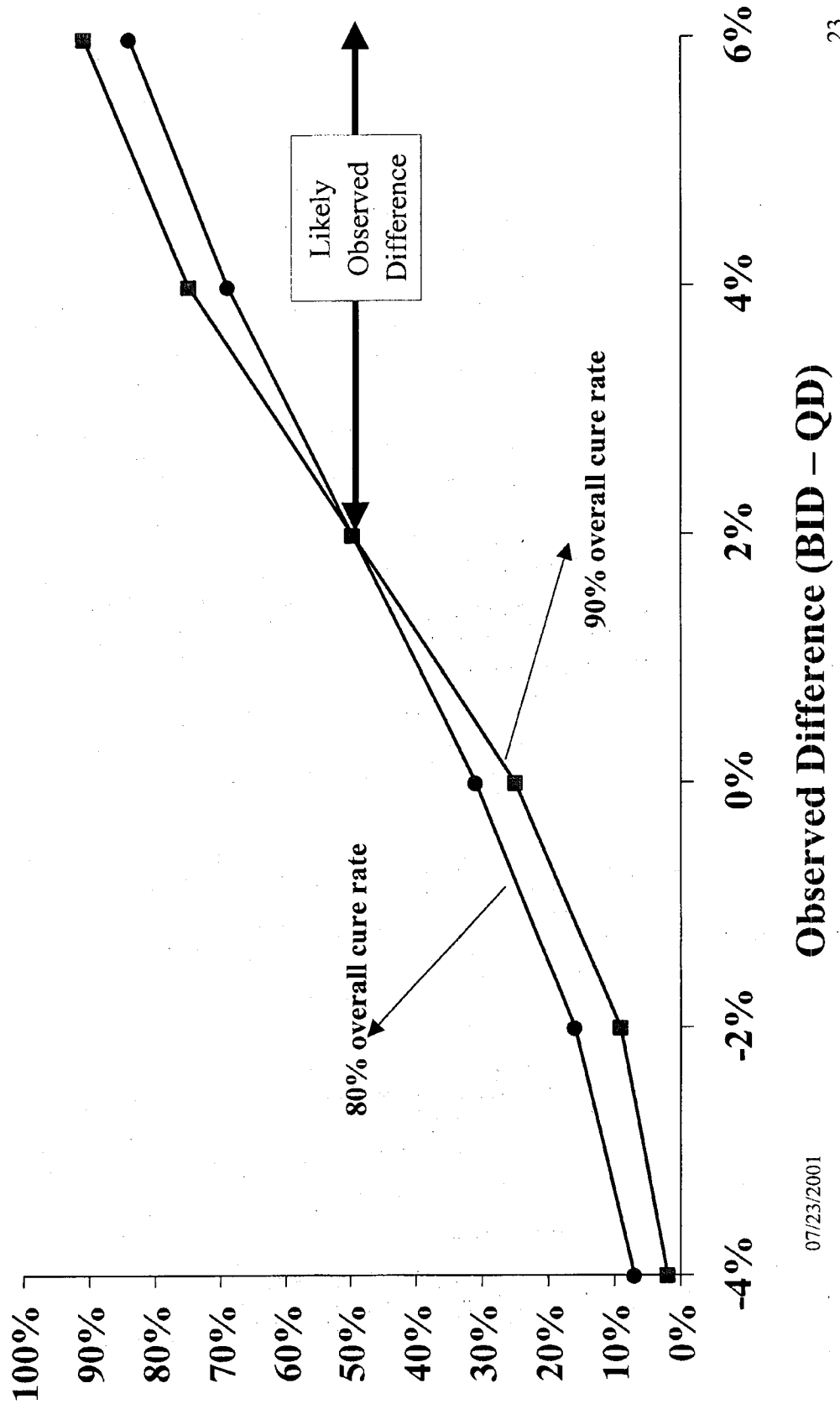
\* 2:1 ratio.  
& Assuming 80% evaluability.

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# Probability that True Difference is Greater Than 2% (N=500, 80% Evaluability)



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# Power and Sample Size

Expected Ph. III Abt. 773 Cure Rate	Observed Ph. II ABT-773 Cure Rate					Likely Ph. II Cure Rate		Likely Comparator Cure Rate
	90%	87%	85%	83%	80%	83%	80%	
90%	97% N=354	71% N=814	41% N=1708	17% N=5039	3% IFN. N=5955	17% N=5039	3% IFN. N=5955	
87%	>99% N=236	93% N=445	75% N=739	49% N=1386	15% N=5955	49% N=1386	15% N=5955	
85%	>99% N=190	98% N=329	90% N=501	97% N=251	82% N=629	97% N=350	82% N=629	
83%	>99% N=158	>99% N=255	96% N=366	97% N=350	82% N=629	97% N=350	82% N=629	
80%	>99% N=124	>99% N=186	>99% N=251	97% N=350	82% N=629	97% N=350	82% N=629	

Power is based on 660 patients with 1:1 ratio and 80% evaluability  
 Sample size is based on 80% power and 80% evaluability and 1:1 ratio

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## Potential Tactics to optimize delayed program timelines

- Ask FDA if we can extrapolate sinusitis data to CAP
  - Low probability given a trial is ongoing
- Ask FDA to unblind CAP data at 350 patients
  - may jeopardise support for AECB 150mg QD dose;
  - risk of excessive statistical penalty if completion also req;
  - if data analysis possible by Sept, answer from FDA in Dec has limited positive impact on timelines
  - risk of FDA requesting ITT instead of PP
- 3 arm study with option to truncate 1 arm
  - No regulatory precedent;
  - statistical risk
  - Low probability of ethics approval
- Continue accrual in existing CAP to reduce burden on Phase3 program.

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# ABT 773 R&D Costs: Tablet

Option	2001 Budget	2001 Var.	Total	Total Var.
Current R&D Cost	88.5		149.8	
BID today	90.0	(1.5)	156.6	(6.8)
Wait for ABS data	80.5	8.0	161.0	(11.2)
Wait for CAP data	79.6	8.9	169.7	(19.9)

Additional costs due to:

- Increased patient numbers 500 patients
- Additional enrollment months/CRO time and resources
- Additional countries/sites

Current Year Additional Costs for QT, Pediatric and Japan \$4,5MM

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## Current Clinical program

- AECB (Pivotal Studies at 150mg QD ongoing)
- Pharyngitis (Pivotal Studies at 150mg QD ongoing)
- CAP and Sinusitis ( 150mg QD vs 150 mg BID)
  - Will support AECB at 150mg QD if equivalent
  - Will contribute to microbiologic data (including resistant pathogens) to meet reg requirements.
  - Will contribute to safety database.
- Making the dose decision today has a significant impact on program

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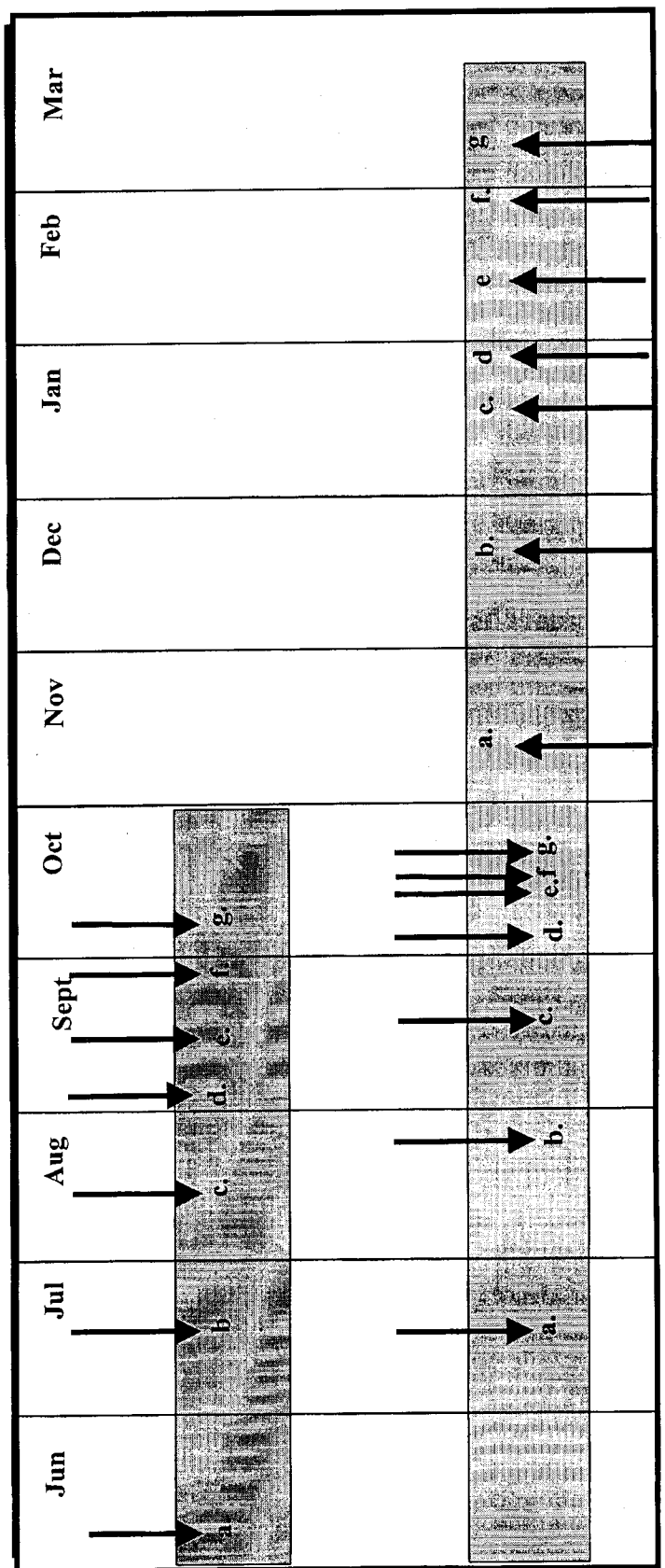
Backups

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Start of Ph3 trials and filing dates dependant on dose decision timeline.

**M00-225: Sinusitis 150 mg QD vs. 150 mg BID M00-219: CAP 150 mg QD vs. 150 mg BID**

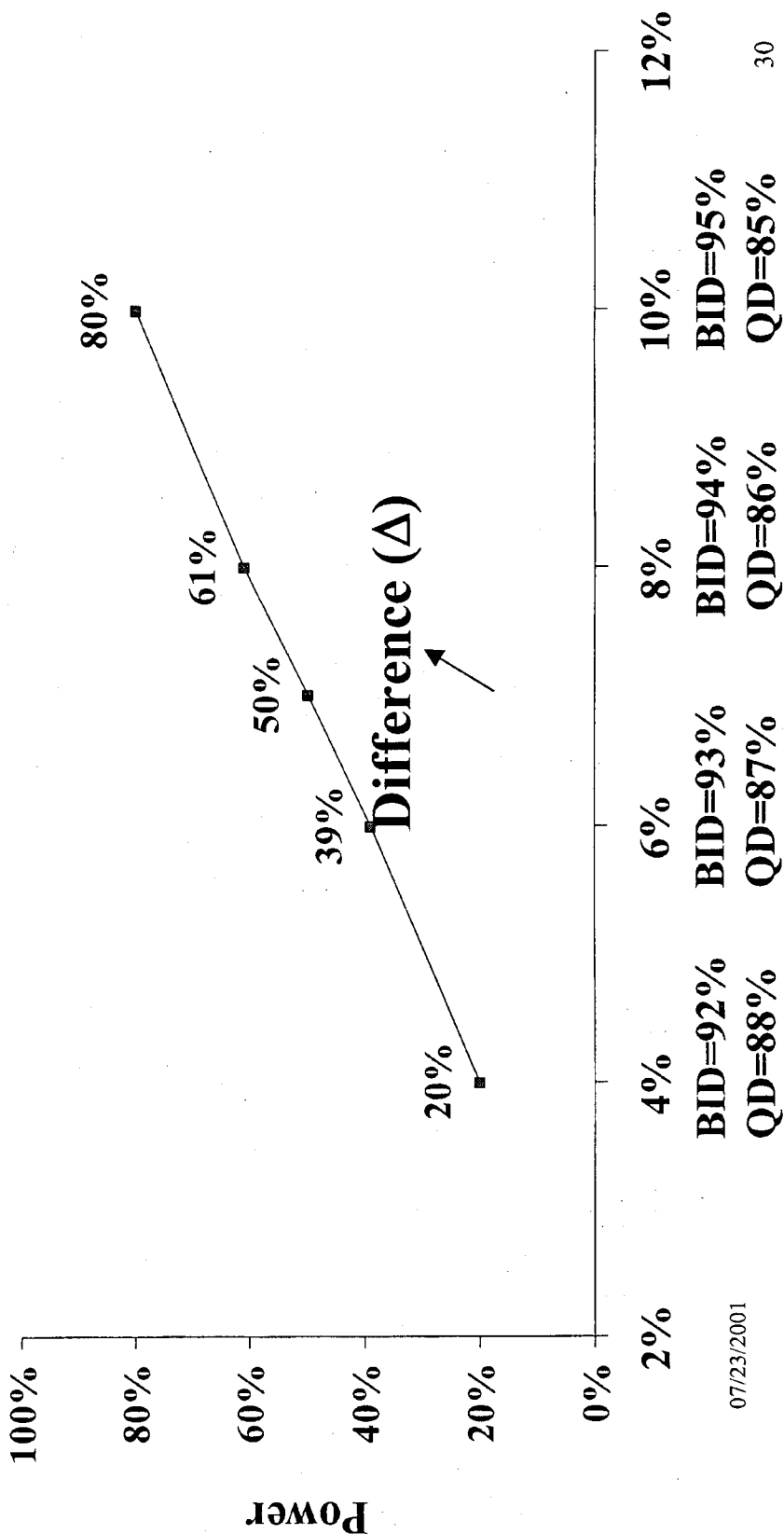


**a . pts enrolled      b. pts completed      c. CRF in house      d. queries resolved**  
**e final classification      f. potential blind break      g. dose decision**

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# Power to Detect $\Delta\%$ Difference with 90% Overall Cure Rate (N=350, 80% Evaluability)



# Dose Decision Outcome

## **Bid Dose Decision for Sinusitis**

Extrapolate BID to CAP

- Regulatory default position for CAP
- Supports potential safety numbers at upper dose

## **QD Dose Decision for Sinusitis**

Need regulatory agreement - 2+ months for FDA

- EU will default to approval/not protocols (Risk)
- Technical probability will work clinical cure in CAP
- Commercial defaults to QD

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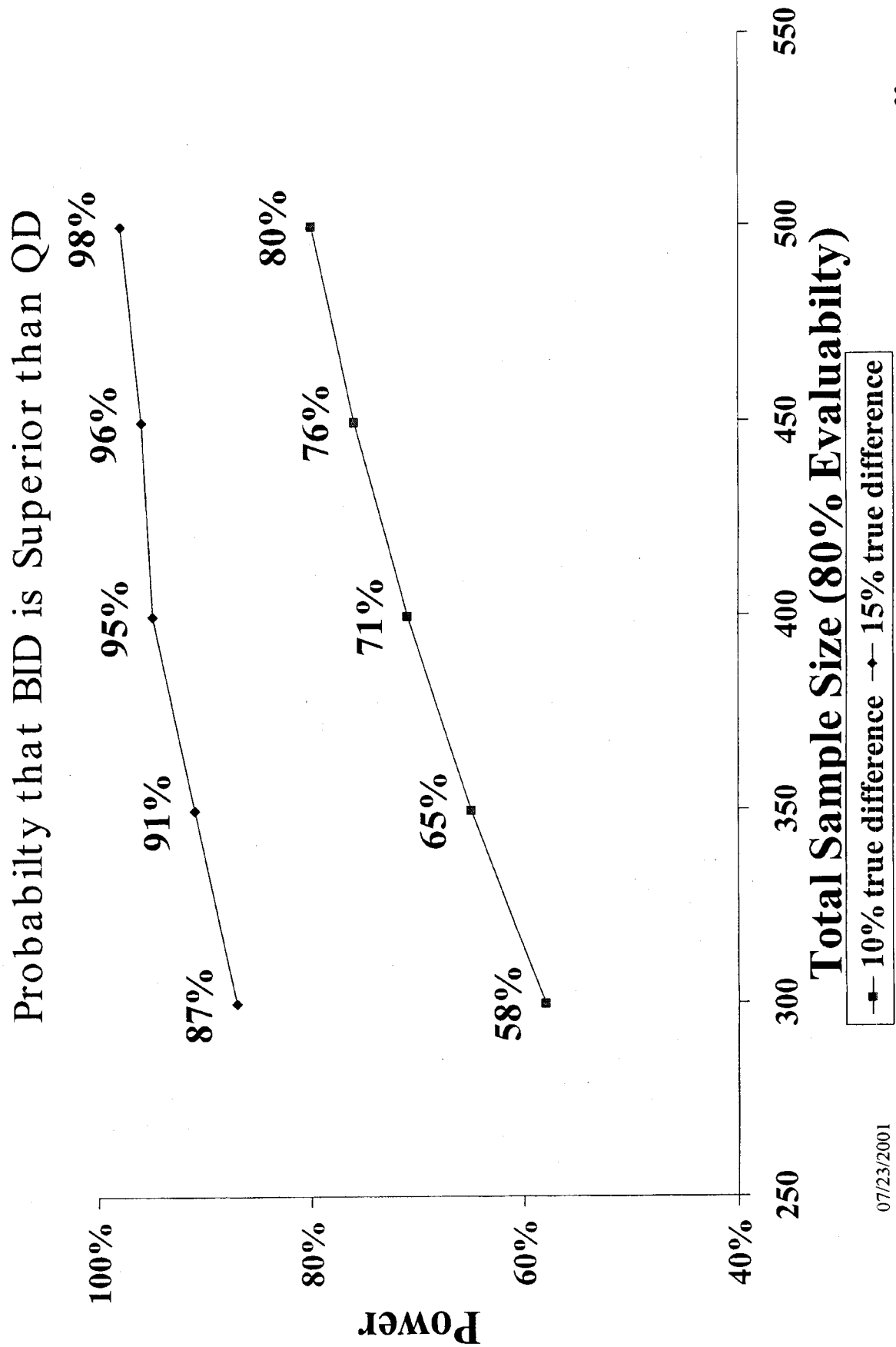
## QD Dose Is Equivalent to BID Dose

- At least 90% overall clinical cure rate is observed for CAP study up to now (approximately 200 patients)
- Historically, clinical cure rate for antimicrobial is around 90%, which implies that it is unlikely two dose regimens are different
- Assuming 90% cure rate for both dose regimens and 80% evalubility, 350 total patients will provide 80% power to demonstrate equivalence per FDA and CPMP equivalent rule (10% rule)

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# PART 3



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## ABT 773 R&D Costs: Other Programs

OTHER PROGRAM COSTS	2001	2002	2003	2004-05	TOTAL
IV FORMULATION	0.5 funded	9.2	9.8	3.9	23.4
PEDIATRIC	1.5	9.0	21.5	22.4	54.4
JAPAN DEVELOPMENT	1.0	2.0	TBD	TBD	TBD
QT STUDY/EKG RE-READS	2.0				

Pediatric program needs to be at least up to Phase2 to get adult indication (\$10.5MM)

IV program offers significant commercial upside with breakeven in 1 year  
QT study and reread ECG's not optional for Adult dose approval.

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## Potential Time or Cost Savings

- CMC activities to be optimized
- 3<sup>rd</sup> study in non-competing countries to cut timeline by allowing only 500 not( 7500)(patients in EU CAP
- Continue enrollment in all sites until ethics approval for pivotals may shorten timeline.
- Given EKG QT study ask FDA to lessen load of EKG's in pivotals will reduce costs.
- Ask Regulatory authorities to consider IV Phase 3 step down program to increase numbers.

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**Phase II Clinicals**  
**Combined ABECB, CAP, ABS**  
**Clinical Response**

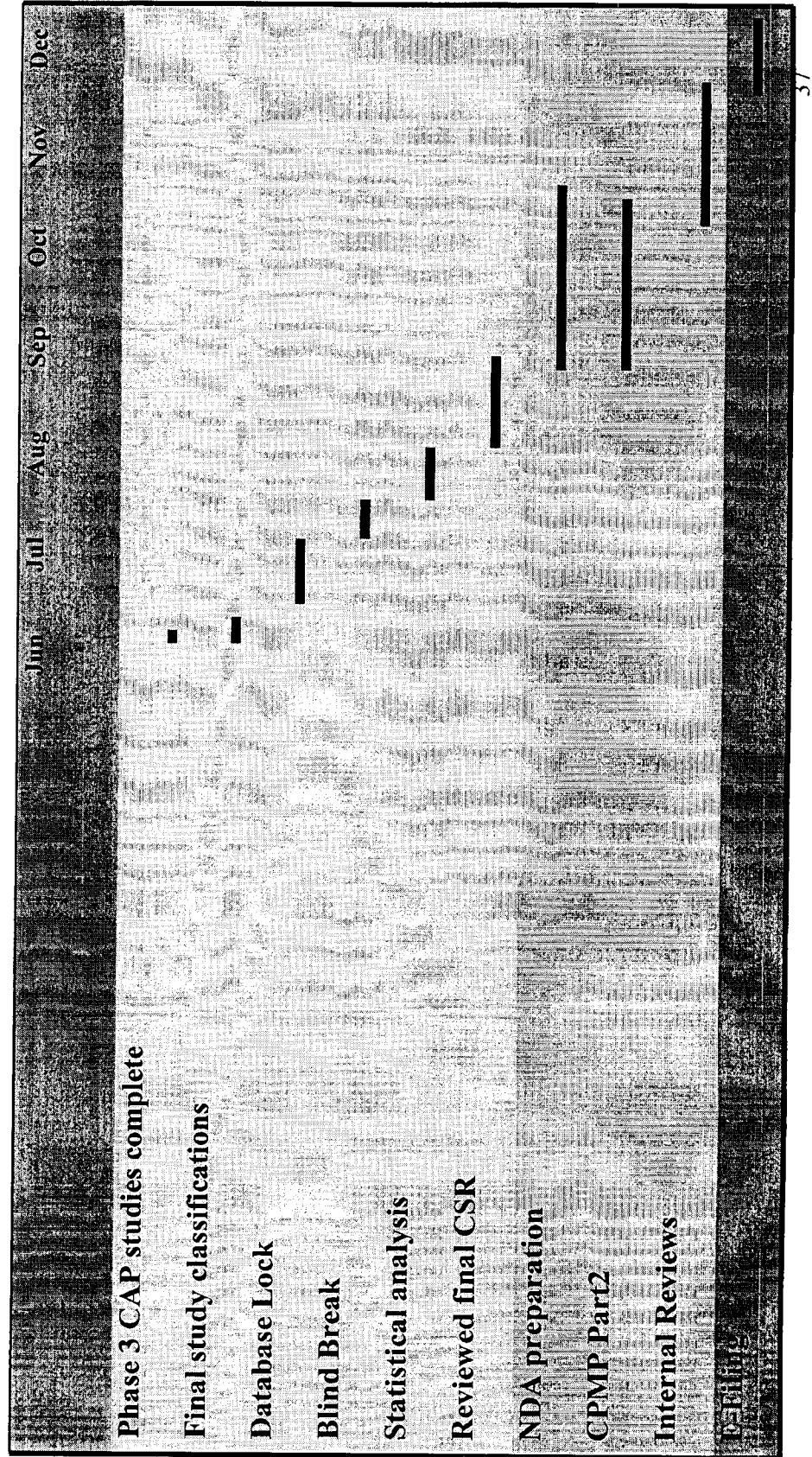
	<b>150 mg</b>	<b>300 mg</b>	<b>600 mg</b>
<b>Clin and Bact. Eval</b>	<b>84%</b> (42/50)	<b>90%</b> (103/115)	<b>88%</b> (106/120)
<b>Clin Eval</b>	<b>88%</b> (168/193)	<b>88%</b> (247/279)	<b>81%</b> (216/265)
<b>ITT</b>	<b>83%</b> (176/211)	<b>82%</b> (259/314)	<b>75%</b> (230/305)

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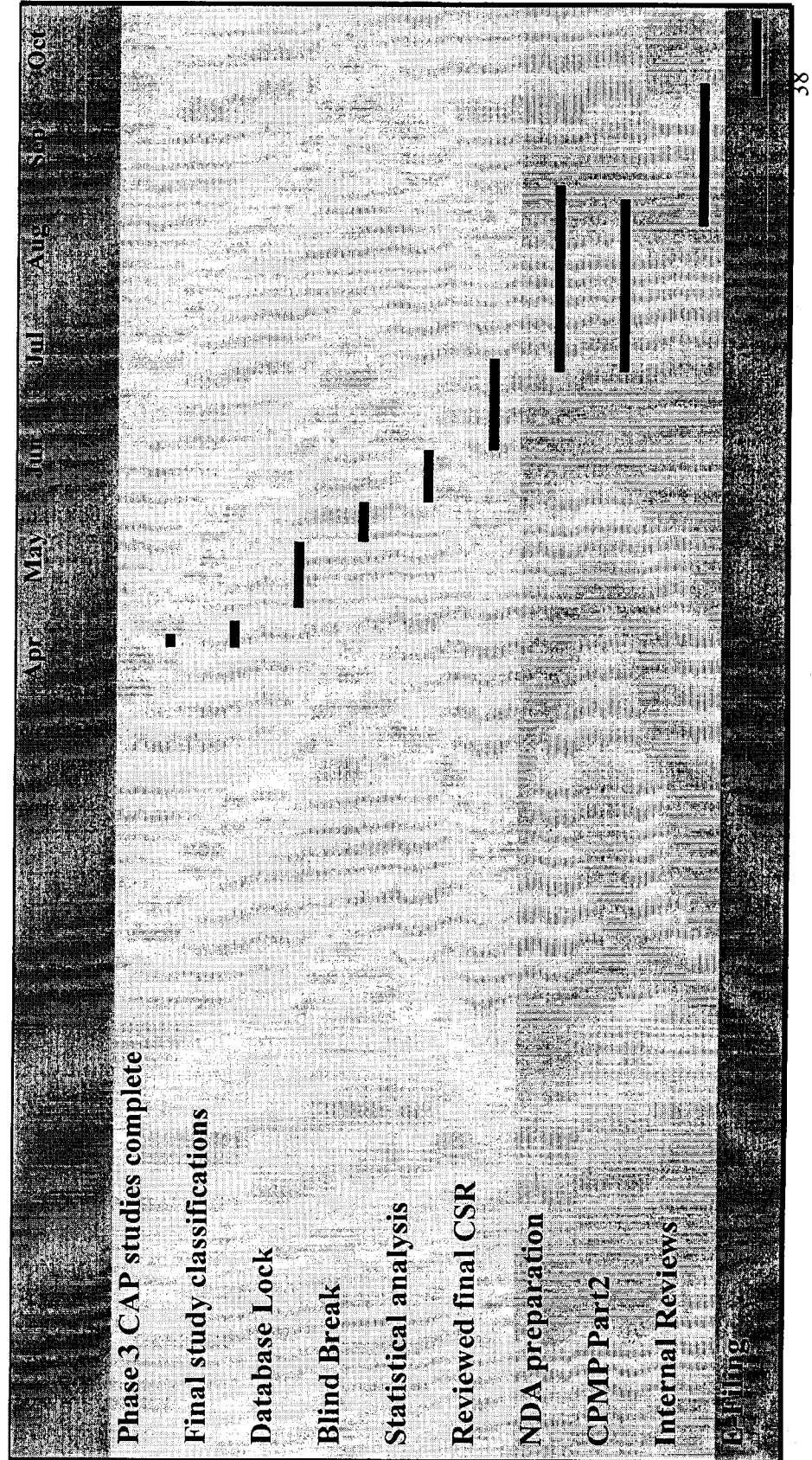


# Critical timeline to filing Using Sinusitis data alone timeline





# Critical timeline to filing Using BID today timeline





Phase II Clinicals  
Combined ABECB, CAP, ABS  
Bacteriological Response

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	87% (13/15)	91% (30/33)	91% (29/32)
<i>M. catarrhalis</i>	84% (16/19)	84% (21/25)	84% (16/19)
<i>H. influenzae</i>	87% (20/23)	94% (33/35)	77% (37/48)
Overall	86% (49/57)	90% (84/93)	83% (82/99)

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Phase II Clinicals  
Combined ABECB, CAP, ABS

**All Adverse Events**

600 mg

300 mg

150 mg

**GI and Taste**

**Taste Perversion**

27% (87/318)

17% (55/322)

4% (8/223)

**Diarrhea**

19% (60/318)

11% (34/322)

10% (22/223)

**Nausea**

26% (83/318)

12% (40/322)

5% (12/223)

**Vomiting**

14% (44/318)

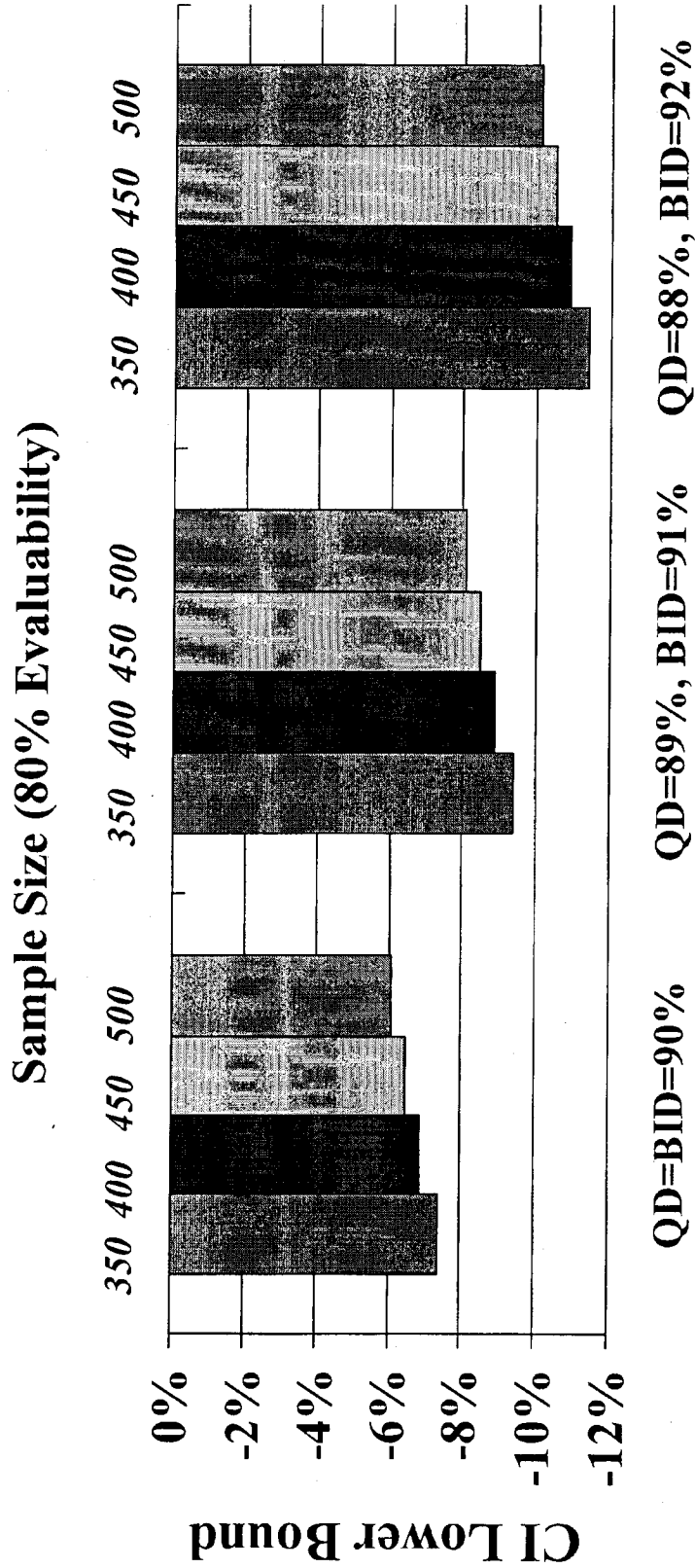
6% (19/322)

2% (4/223)

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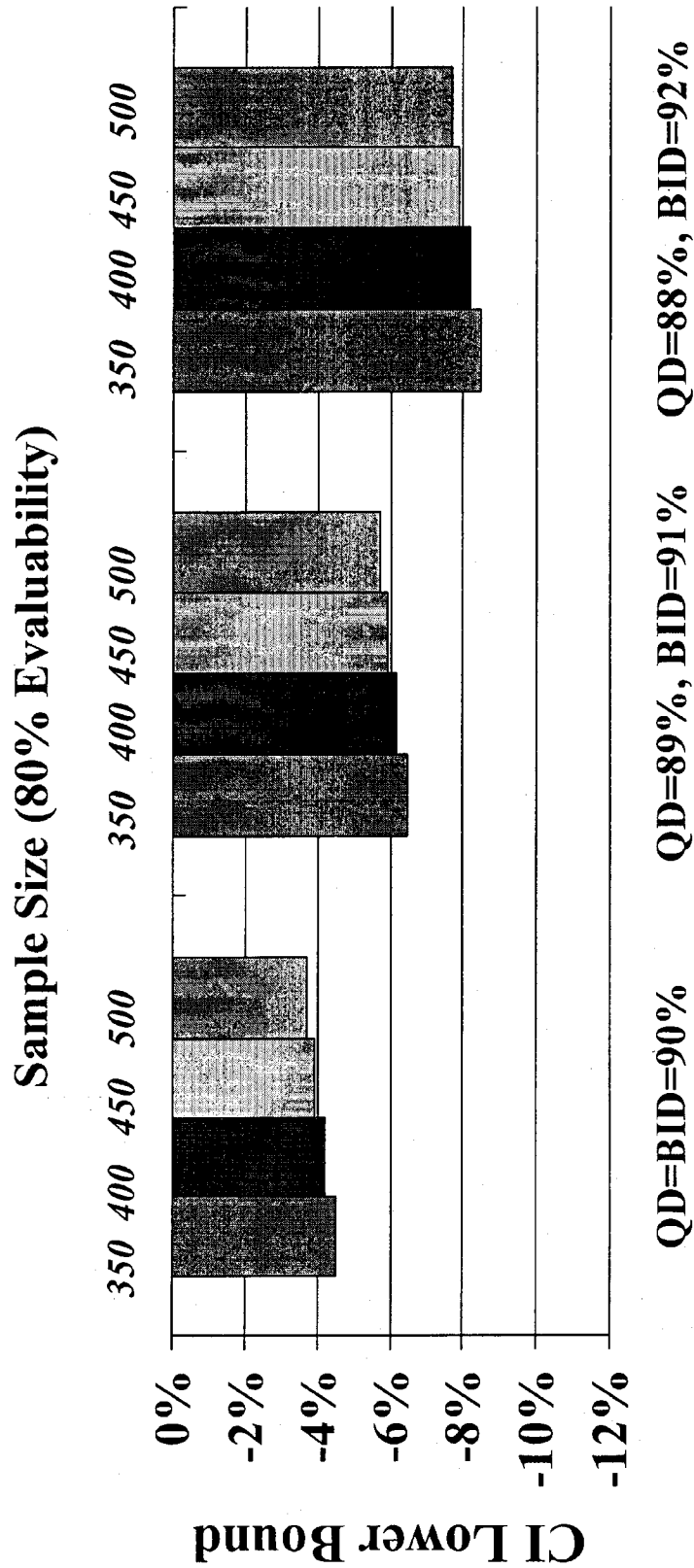
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# Two Sided 95% Lower Confidence Bound of Difference (150 QD – 150 BID)



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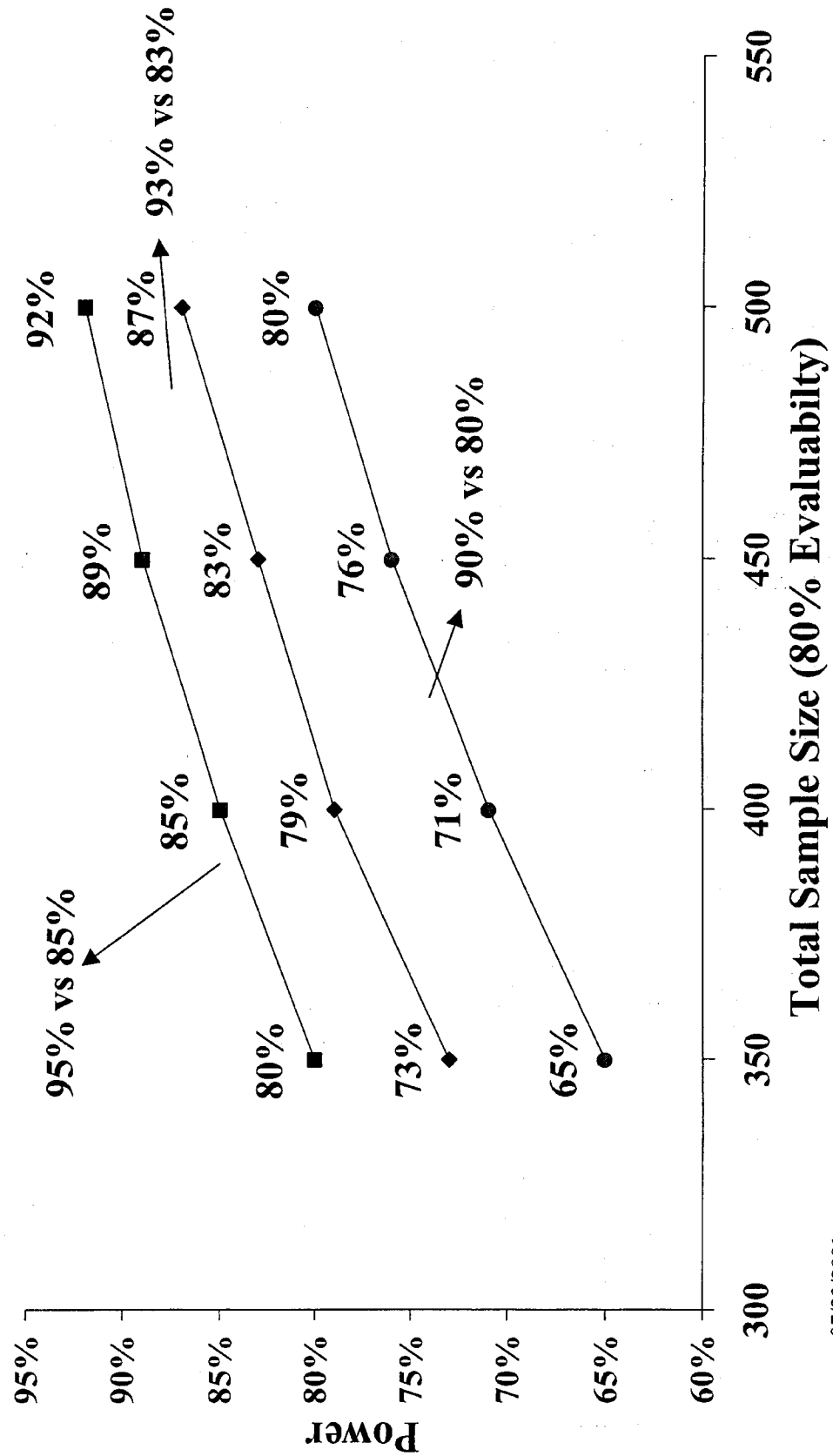
# Two Sided 75% Lower Confidence Bound of Difference (150 QD – 150 BID)



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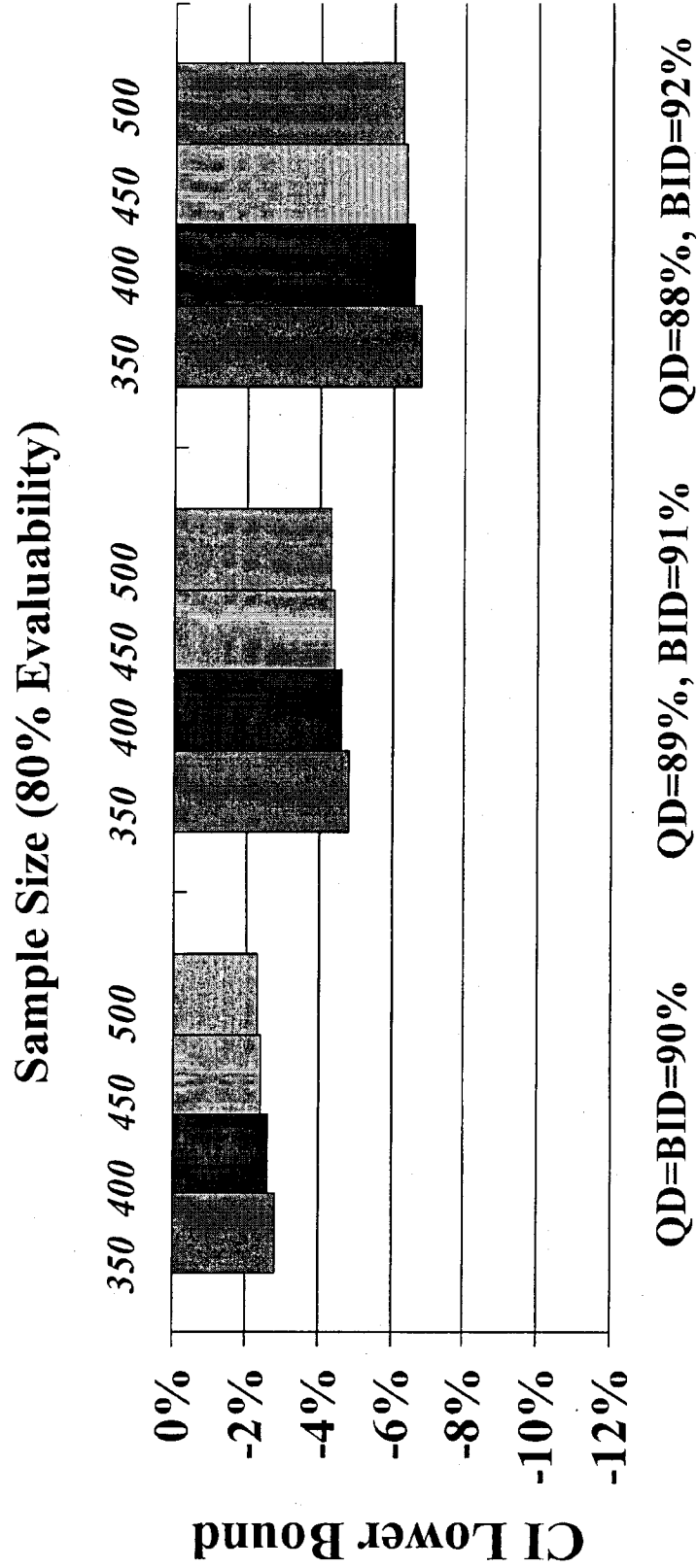
Current Data supports a rational reason to justify unblinding CAP Data

## Power to Detect 10% Difference



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# Two Sided 50% Lower Confidence Bound of Difference (150 QD – 150 BID)



## Observed Cure Rates

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## Pediatric - Summary

- FDA requires a Pediatric Development Program
  - Pediatric referral filed to FDA last year
  - Critical to show FDA compliance with regulation of Pediatric program for NDA (tablet) approval
- Two formulations were developed and tested in humans
  - Bio-equivalence was  $< 80\%$  ( $\sim 78\%$ )
- Several tests to evaluate flavor:
  - ABT-773 between clarithromycin (worst) and azithromycin (best)
- Pediatric dose is estimated to be 2 times the final adult dose

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## Pediatric - Summary

- Revised pediatric program:
  - Two or three new formulation under development
  - Dose will be adjusted to achieve desire plasma concentrations

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# Pediatric Development Plan

## Phase 1:

- 1- Single dose bio study:
  - 2 or 3 pediatric and reference formulations (IR-E)
- 2- Open IND with the following Multiple dose study:
  - pediatric selected formulation and reference (IR-E)
  - 300 mg QD for 5 days

## Phase 2:

- 1- Otitis Media study versus Upper Resp Tract Infect study (otitis and pharyngitis):
  - a. Children 1 to 12 years of age
  - b. Three doses: 2.5, 5, 10 mg/kg/d (lower higher dose to 7.5 mg/kg)
  - c. Otitis media with double tap and middle ear fluid concentrations
  - d. Plasma samples
  - e. Maximum dose: 400 mg day

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# PART 4

Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

1. Complete current ABS & CAP dose-ranging trials and then make dose decision. (Use ABS & CAP dose-ranging data)
2. Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. (Use ABS dose-ranging data only)
3. Select the BID dose today for ABS & CAP Ph III pivotal. (Select BID today)
4. Select the QD dose today for ABS & CAP Ph III pivotal. (Select QD Today)
5. Develop BID in CAP & ABS for EU; Develop QD for US. (QD in the US & BID in the EU)
6. Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator. (Phase III 3-arm CAP & ABS pivotal). Variation: drop arm on result availability

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## Pediatric Development Plan

- Go/No go
- Phase 3:  
3 studies:

Otitis media











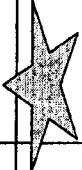
Pneumonia (IV?/?/PO)

Pharyngitis

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# BID today Start Pivotal Trials

Activities	July	Aug.	Sept.	Oct.	Nov.
Select CRO					
Draft Protocol					
Protocol Sign Off					
Prep FDA submission					
FDA submission/approval CAP blind break					
Dose Decision + 1 Day					
Reg. Docs. Approved					
IRB approvals					
Drug Packaging/both options					
Site initiations					
First Patient enrolled US/EU + 6					
				CAP & Sinusitis*	

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## Pediatric – Summary: Issues

1. ABT-773 presentation 2 concentrations (example: 150 mg/5mL and 300 mg/mL) vs. 1 concentration (either)
2. Blinding for phase 2 studies
3. Need External Safety Review for Phase 2 (tolerability of higher dose)
4. Final ages: 6 months up 12 years
5. Final dose selection will be impacted by the dose selection from adults (BID vs. QD)

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SAE Summary  
Phase 2b

• M99-048 AECEB	(6/384)	2%
• M99-053 Sinusitis	(3/292)	1%
• M99-054 CAP	(14/187)	7.5%
• Total	(23/863)	3% *

\*2 Expedited Reports

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SAE Summary  
Phase 3 (IND Studies)

• M00-216 AECB	(15/456)	3.3%
• M00-219 CAP	(21/343)	6.1%
• M00-223 Pharyngitis	(5/522)	1.0%
• M00-225 Sinusitis	(4/485)	0.8%
• Total	(45/1805)	2.45%

\* As of July 08, 2001

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Pregnancies

- M00-223
  - 3 SUBJECTS\*
- M00-225
  - 2 SUBJECT
- Total 5 pregnancies

\* One subject had an elective abortion

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*Abbott Laboratories  
Anti Infective Venture  
Global Pharmaceutical Research & Development*

Stan Bukofzer, MD  
Head, Anti Infective Venture  
July 25, 2001

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- Agreed on best dose probability

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## Potential Implications of 150mg QD vs 150mg BID put in slide of pros and cons

- Having embarked on a dose deficiency trial, we might default US to await outcome
- Based on PK/PD profile, skepticism by medical advisors and regulatory authorities as to success of QD dose, however, commercial favor QD dosing
- Concern that QD dose might encourage emergence of resistance
- Split dosing will go against regulatory mainstream (EU > US) and could adversely affect safety numbers at 150 mg BD dose
- ABS data cannot necessarily be used to extrapolate to CAP dose for EU and possibly for US

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# Power to Demonstrate Equivalence in a Phase 3 Trial

	Cure Rate 90%			Cure Rate 85%			Cure Rate 80%		
True Diff.	500	660	750*	500	660	750*	500	660	750*
0%	92%	97%	97%	80%	90%	90%	71%	82%	82%
2%	73%	84%	85%	59%	67%	72%	50%	62%	63%
4%	46%	57%	59%	36%	42%	47%	31%	38%	39%

\* 2:1 ratio.  
& Assuming 80% evaluability.

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Preliminary Phase III Blinded Data  
All Adverse Events

	<b>Taste</b>	<b>Nausea</b>	<b>Diarrhea</b>	<b>Vomiting</b>
<b>Bronchitis 150 QD vs AZI</b>	0.7% (1/130)	3.8% (5/130)	7.6% (10/130)	0.7% (1/130)
<b>CAP 150 QD or 150 BID</b>	5.1% (3/58)	8.6% (5/58)	5.1% (3/58)	6.8% (4/58)
<b>Pharyngitis 150 QD vs Pen</b>	2.2% (3/135)	14.0% (19/135)	6.6% (9/135)	6.6% (9/135)
<b>Sinusitis 150 QD or 150 BID</b>	5.7% (7/122)	9.8% (12/122)	4.0% (5/122)	3.2% (4/122)
<b>TOTAL</b>	<b>3.1% (14/445)</b>	<b>9.2% (41/445)</b>	<b>6.0% (27/445)</b>	<b>4.0% (18/445)</b>

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Compares favorably to Clari and Ketek profiles

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## Factors Affecting 150 mg QD Dose Selection

<b>For</b>	<b>Against</b>
<ul style="list-style-type: none"> <li>• All subjects available for safety evaluation</li> <li>• Favorable results of CAP may be used to support bronchitis</li> <li>• ↓ risk of unfavorable tolerability profile</li> <li>• ↓ risk of QT effect</li> </ul>	<ul style="list-style-type: none"> <li>• Based on Pk/PD modelling               <ul style="list-style-type: none"> <li>– Higher Regulatory hurdle for demonstrating efficacy</li> <li>– Advisors skepticism of efficacy in CAP</li> </ul> </li> <li>• Concern regarding emergence of resistance</li> </ul>

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## Factors Affecting 150 mg BID Dose Selection

For	Against
<ul style="list-style-type: none"><li>• Based on Pk/PD higher probability of achieving efficacy endpoints in Ph 3.</li><li>• Greater acceptance by advisors and Reg agencies</li><li>• Perception of less likelihood of BID resulting in emergence of resistance</li></ul>	<ul style="list-style-type: none"><li>• Potential for more unfavorable tolerability profile</li><li>• Less safety margin for QT effect given potential CYP3A interactions</li><li>• Some risk for adequacy of safety database in a two-dose program</li><li>• Cost of goods higher</li></ul>

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## Tactics to maximize use of Winter '01

A BID decision today (both CAP/sinusitis)

A BID decision for CAP if Sinusitis is BID

If sinusitis QD with CAP QD based on 350 pats,

US requires FDA agreement to break blind.(end Sept) Data likely to favor CAP QD.

Downside risk of being told to wait on blind break

Delaying request to FDA until after sinusitis data will cause missed season

AI : QD decision requires national Agency meetings, but with supportive data unlikely to be time delaying. Will require starting at risk

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## How to Make Dose Decision (Sinusitis)

If 10% difference, clinical cure per protocol → Decision

If less than 10% difference, consider clinical and bacterial cure as above

If more than 10% difference → Decision

If less then, >80% for one arm clinical and bacterial cure → Decision

If less than that, default to QD → Decision

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ABT-773 Preliminary Phase III Blinded Data  
All Adverse Events

	<b>Taste</b>	<b>Nausea</b>	<b>Diarrhea</b>	<b>Vomiting</b>	<b>Headache</b>
Bronchitis 150 QD	1.5% (6/397)	3.5% (14/397)	10.8% (43/397)	0.7% (3/397)	6.5% (26/397)
CAP 150 QD or 150 BID	3.8% (8/207)	6.2% (13/207)	9.1% (19/207)	5.3% (11/207)	10.1% (21/207)
Pharyngitis 150 QD	1.9% (9/453)	8.8% (40/453)	8.1% (37/453)	4.4% (20/453)	10.5% (48/453)
Sinusitis 150 QD or 150 BID	5.2% (16/303)	5.6% (17/303)	5.6% (17/303)	2.3% (7/303)	5.6% (17/303)
<b>TOTAL</b>  07/23/2001	2.8% (39/1360)	6.1% (84/1360)	8.5% (116/1360)	3.0% (41/1360 )	8.2% (112/1360)

## Impact of CAP data on dose decision

- Imposes a delay to Sept 02 start of pivotals in CAP and sinusitis
- Predictive value of CAP data is essentially similar to sinusitis data ( same dynamics of clinical trial data)
- Therefore no significant benefit due to delay in expected launch date
- No program cost advantage identified.

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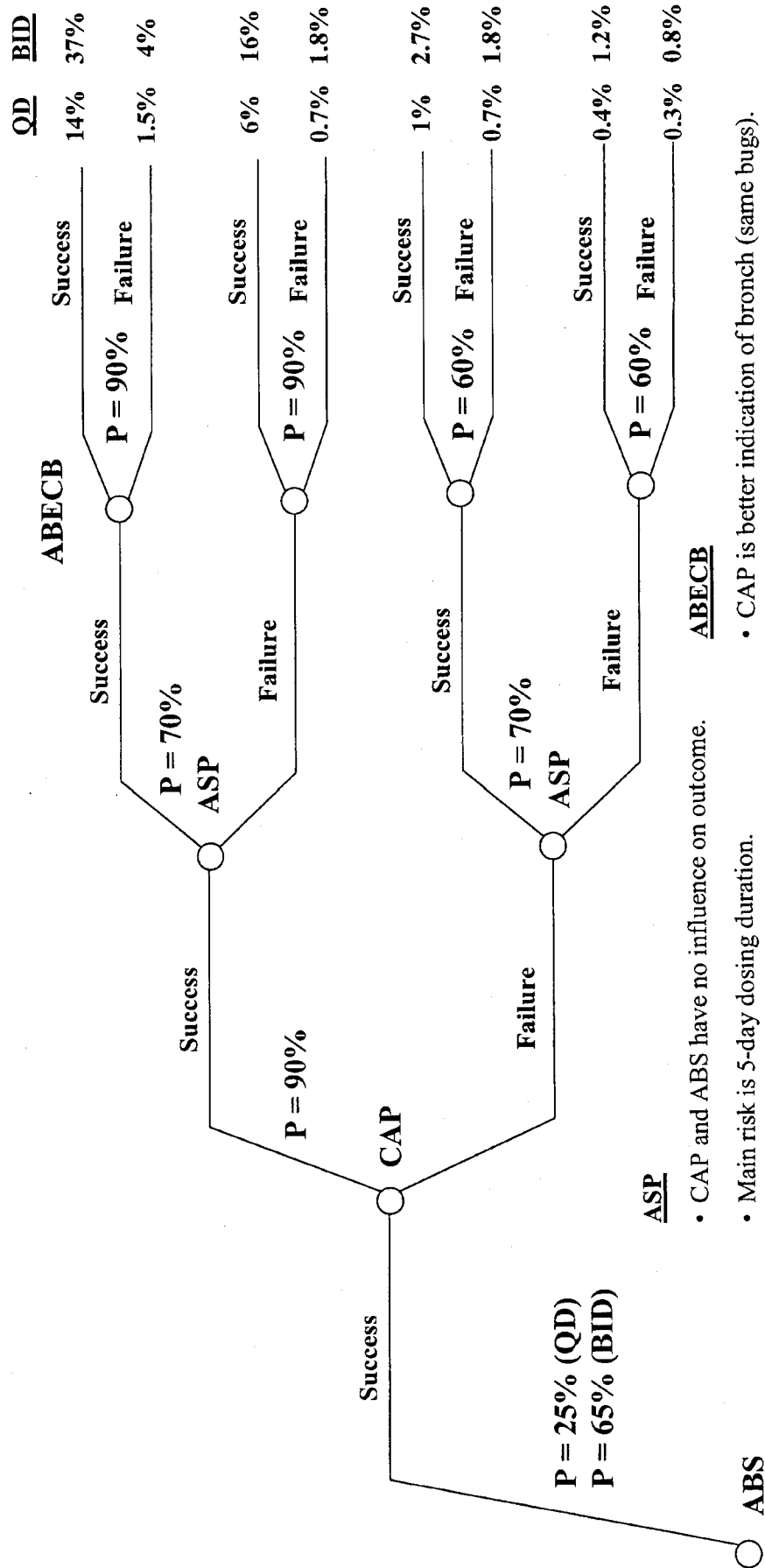
DSG Backups

07/23/2001

# ***Efficacy: Co-variance between indications (ABS success)***

Asset: ABT-773  
Alternative: All  
Provided By: Joaquin Valdes  
Date: 5/7/01

- Is the order of indications logical? From most difficult to easiest?
- Are the assessments different for QD vs. BID?



**ASP**

**ABECB**

• CAP and ABS have no influence on outcome.

• Main risk is 5-day dosing duration.

• Endpoint is eradication rather than clinical cure.

• Only need to treat *S. pyogenes*

• CAP is better indication of branch (same bugs).

• CAP and ABECB are related.

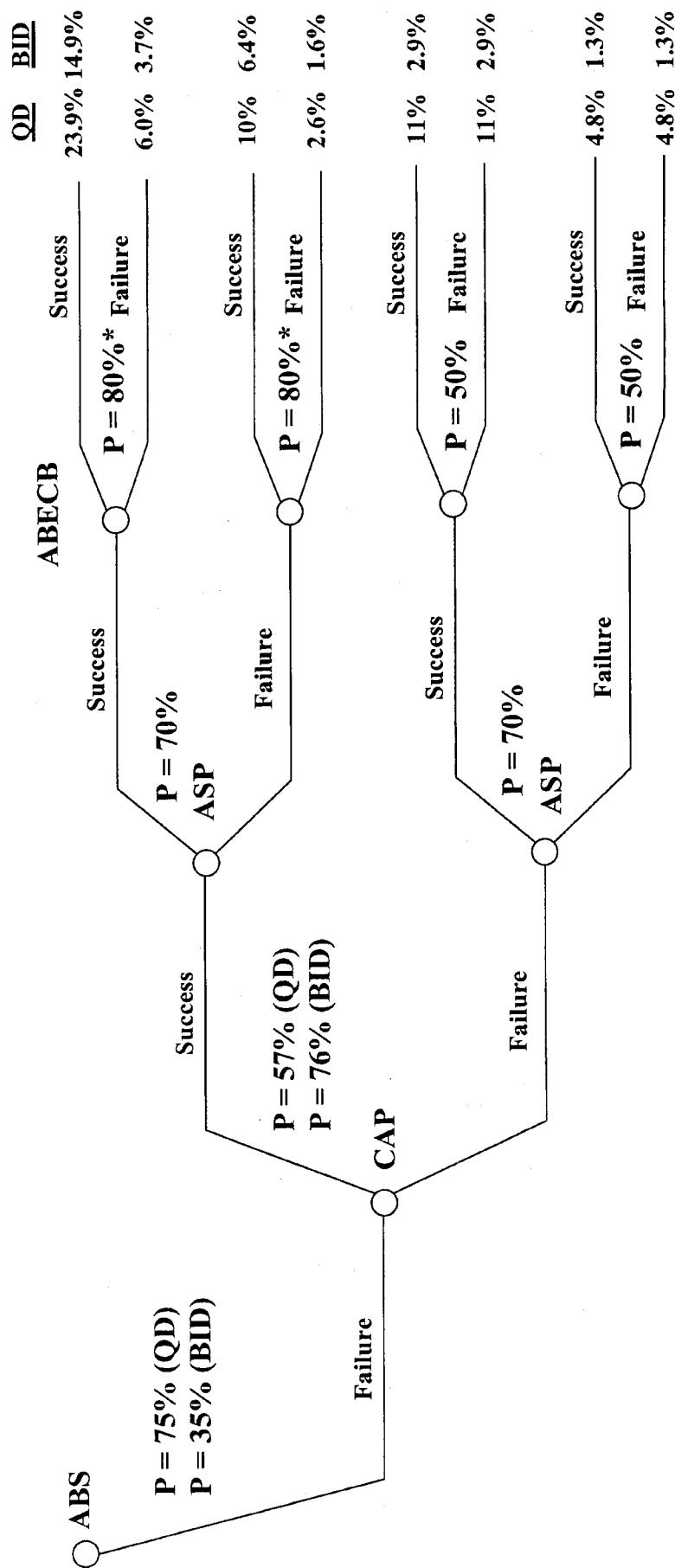
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Asset: ABT-773  
 Alternative: All  
 Provided By: Joaquin Valdes  
 Date: 5/7/01

# *Efficacy: Co-variance between indications (ABS failure)*

- Is the order of indications logical? From most difficult to easiest?
- Are the assessments different for QD vs. BID?



\* Calculations based on prior assessments  
 07/23/2001



Insert Steve's updated commercial assumptions slide

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# Probabilities of regulatory approval (US).

ABS	CAP	ASP	ABEC B	Regulatory Prob	
				With resistance claim	Without resistance claim
✓	✓	✓	✓	0.95	0.90
✓	✓	✓		0.85	0.80
✓	✓		✓	0.95	0.90
✓	✓			0.85*	0.75*
✓		✓	✓	NA	0.5 0.1
✓		✓		NA	0.1 0
✓			✓	NA	0.1 0
✓				NA	0 0
	✓	✓	✓	0.85*	0.75*
	✓	✓		0.50*	0.25*
	✓		✓	0.70*	0.40*
	✓			0.50*	0.25*
		✓	✓	NA	0
		✓		NA	0
			✓	NA	0
01/23/2001				NA	0

• Assessments assume a perfectly clean safety database (except where indicated).

• All assessments assume 1<sup>st</sup> line treatment.

• Yellow boxes assume “clari-like” safety profile. Probabilities are significantly lower because the absence of CAP reduces the benefit/risk.

• Assessments with an asterisk (\*) indicate outcomes where additional safety data will be needed for approval (to complete the safety database).

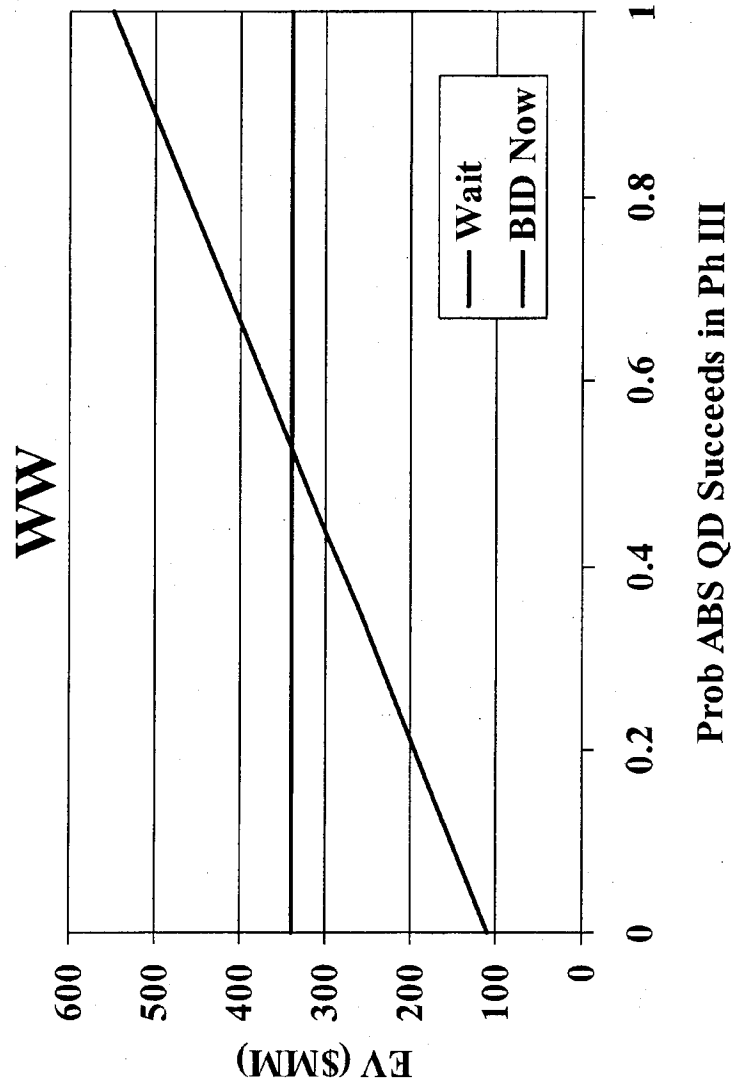
• Resistance was deemed approvable only in the case of CAP success (NA is shown where CAP fails).

# Probabilities of regulatory approval (EU).

ABS	CAP	ASP	ABEC B	Regulatory Prob	
				Without resistance claim	With resistance claim
✓	✓	✓	✓	0.90	0.95
✓	✓	✓		0.70	0.80
✓	✓		✓	0.70	0.80
✓	✓			0.50	0.60
✓		✓	✓	0.10	0.10
✓		✓		0.10	0.10
✓			✓	0.10	0.10
✓				0.10	0.10
	✓	✓	✓	0.20	0.30
	✓	✓		0.20	0.30
	✓		✓	0.20	0.30
	✓			0.20	0.30
		✓	✓	0.05	0.05
		✓		0.05	0.05
			✓	0.05	0.05
				0	0

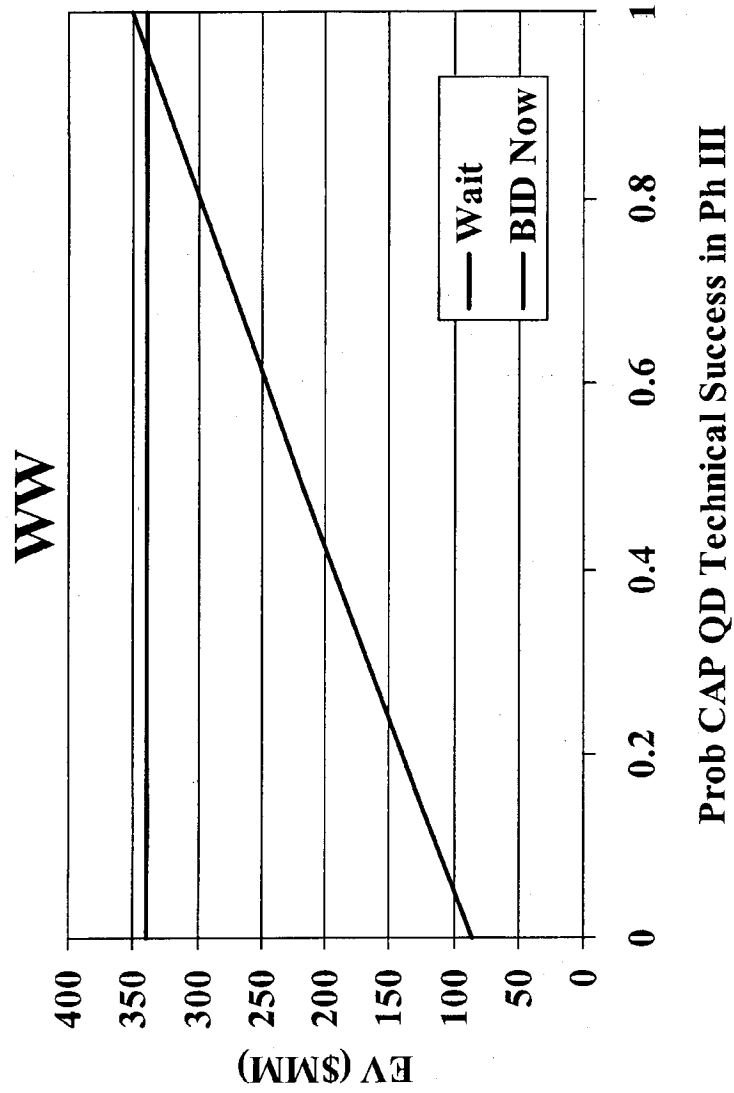
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# Sensitivity to ABS QD prob in Ph III



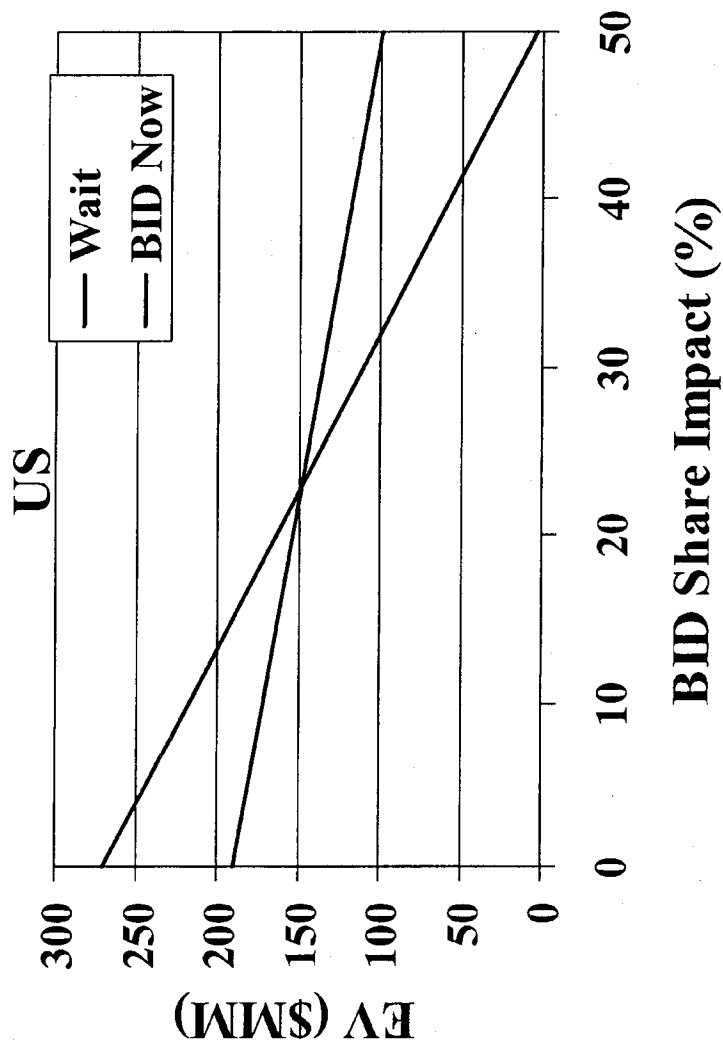
07/23/2001

# Sensitivity to CAP QD risk in Ph III



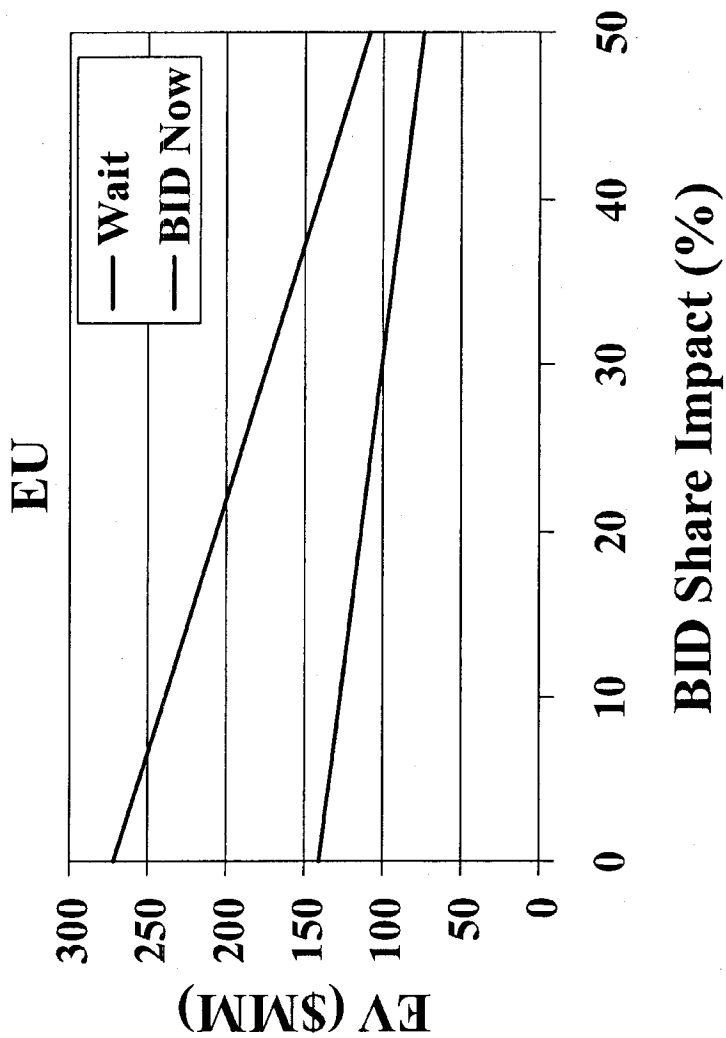
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# Sensitivity to share impact



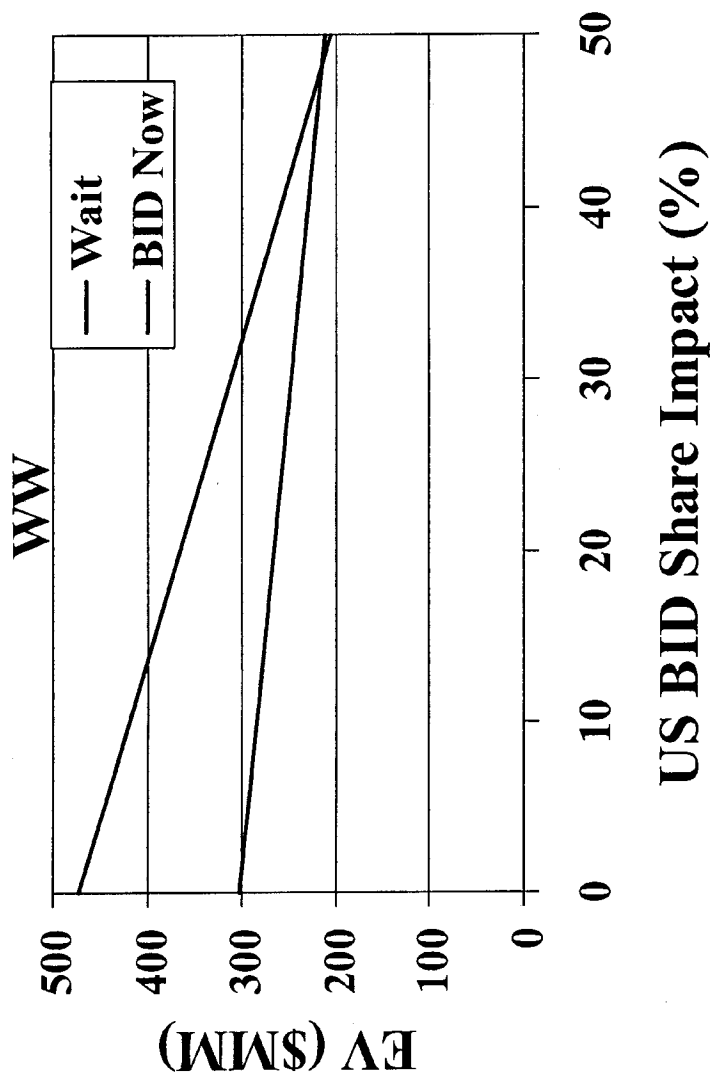
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# Sensitivity to share impact



07/23/2001

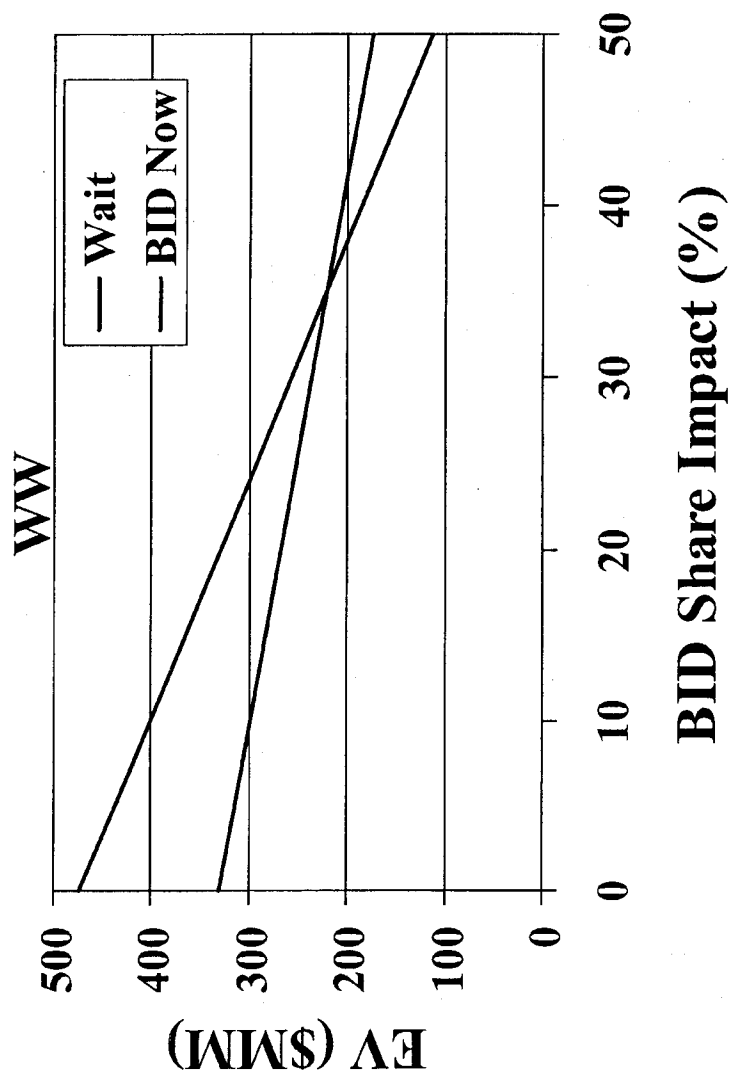
# Sensitivity of WW value to US share impact



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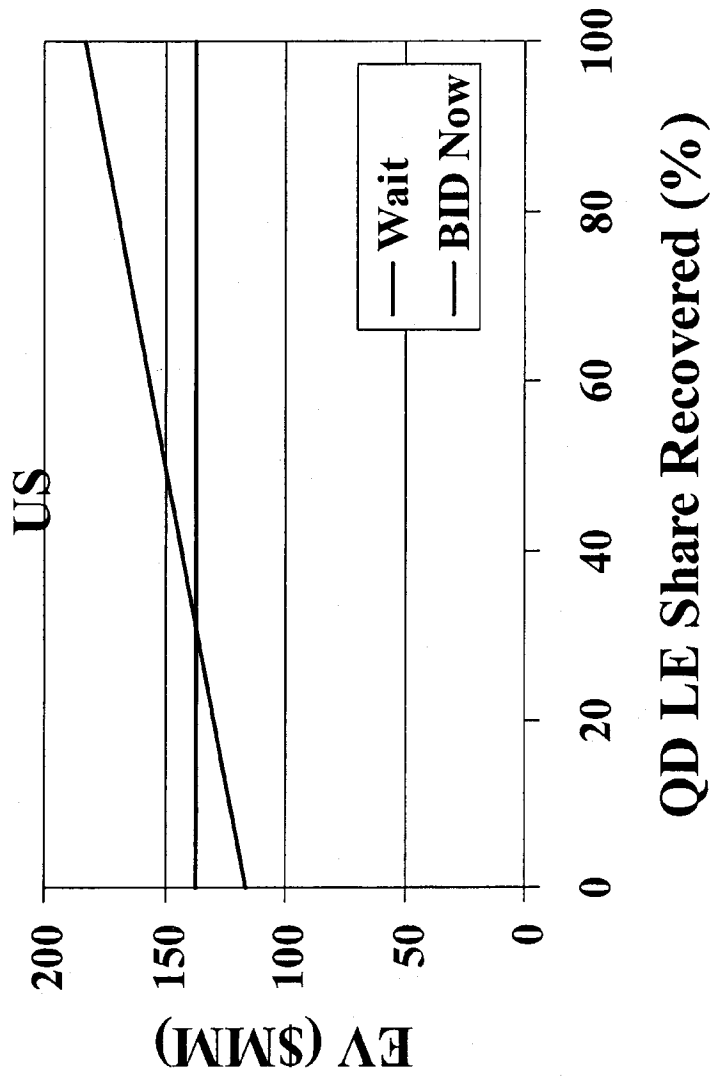


# Sensitivity to share impact



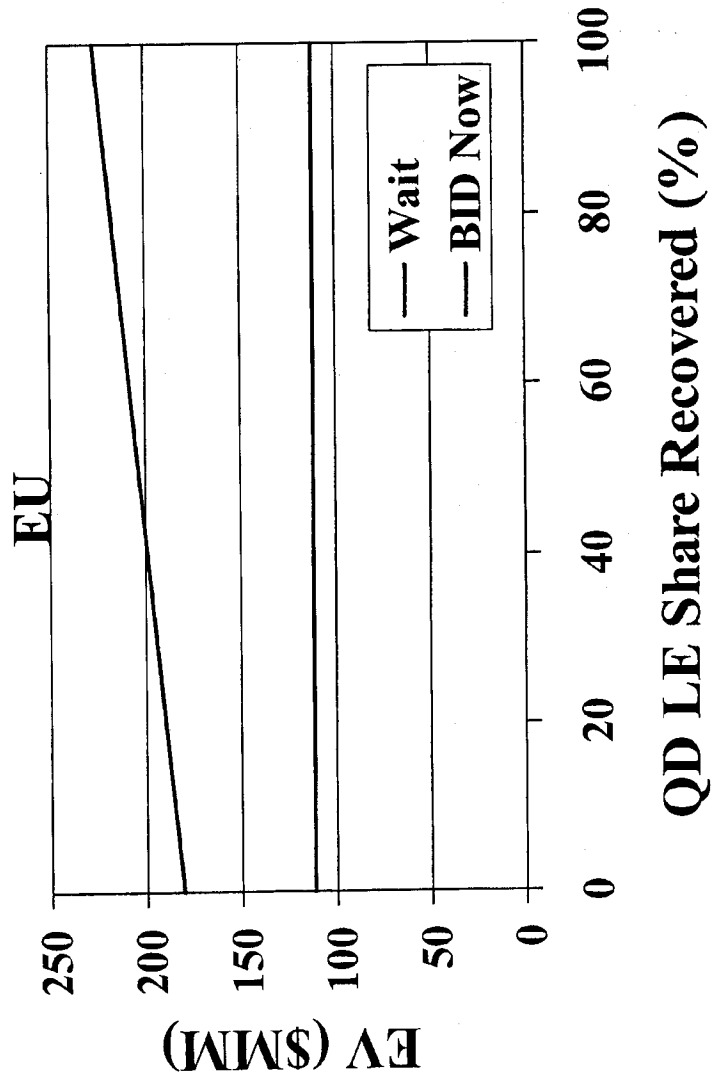
07/23/2001

# Sensitivity to QD LE



07/23/2001

# Sensitivity to QD LE



07/23/2001